Recent Advances in Endometrial Cancer

Sumita Mehta
Bindiya Gupta
Editors

Springer

Recent Advances in Endometrial Cancer

Sumita Mehta • Bindiya Gupta
Editors

Recent Advances in Endometrial Cancer

Springer

Editors
Sumita Mehta
Department of Obstetrics & Gynecology
Babu Jagjivan Ram Memorial Hospital
New Delhi
India

Bindiya Gupta
Obstetrics and Gynecology
UCMS & GTB Hospital
Delhi
India

ISBN 978-981-15-5316-5 ISBN 978-981-15-5317-2 (eBook)
https://doi.org/10.1007/978-981-15-5317-2

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Preface

Endometrial cancer is the most common malignancy of the female genital tract, and its incidence is on the rise primarily due to changing lifestyles. This book is an attempt to present all the recent advances and updates in endometrial cancer. The topics are well researched and written by experts in the field of oncology.

The first part deals with the epidemiological trends and etiology. The majority of endometrial cancers have a well-defined precursor lesion, and their specific management has been discussed in this part. With advances in genetic testing, diagnosis of hereditary endometrial cancer has become easier and guidelines have been outlined in the screening and management of these genetic syndromes.

Part II will update the reader in all aspects of management including recent advances in surgery and adjuvant therapy. An important aspect studied nowadays is the increasing role of sentinel lymph node mapping in order to reduce the morbidities associated with complete lymphadenectomy. Although still in research setting, level one evidence is fast accumulating to include it as standard of care. As endometrial cancer is affecting younger women who have not completed their family, conservative management has been discussed in detail in this book.

Part III covers the newer advances in molecular classification and advances in immunotherapy. miRNAs as a group are emerging as biomarkers for the early diagnosis of endometrial cancer, and their role in detection and planning treatment strategies has been discussed. Management and therapeutic responses of recurrent endometrial cancer and non-endometrioid endometrial cancer have also been dealt with in separate chapters. Chapters on uterine sarcomas and STUMP which are other important uterine tumors have also been included in the book to make it holistically complete for the convenience of the readers.

We thank the authors for their contribution and sincerely hope that the book will equally benefit young upcoming gyn-oncologists and experienced seniors. Our attempt is that it will serve as an easy-to-read handbook for its readers.

New Delhi, India

Sumita Mehta
Bindiya Gupta

Contents

About the Editors

Sumita Mehta completed her postgraduate degree at Maulana Azad Medical College, Delhi University, and is currently a senior specialist in charge of the Department of Obstetrics and Gynecology at BJRM Hospital, Delhi. She was the secretary of the Indian Society of Colposcopy and Cervical Pathology (ISCCP) and is a certified trainer for colposcopy for the state of Delhi as well as the International Agency for Research on Cancer (IARC). She has conducted several colposcopy workshops all over India and has delivered numerous lectures in various academic forums. She is the editor of 8 books and has published over 75 papers in respected national and international journals. She is on the editorial board of the *Journal of Obstetrics and Gynecology Forecast* and *Heliyon* and is a reviewer for several international journals.

Bindiya Gupta completed her postgraduate degree at the All India Institute of Medical Sciences, Delhi, and is currently an Associate Professor at the Department of Obstetrics and Gynecology at Guru Teg Bahadur Hospital, Delhi. She has received numerous awards, including the Federation of International Gynecologist and Obstetrics (FIGO) award for best paper from a developing country. She has also been awarded the commonwealth fellowship in gyn-oncology and is pursuing her training in Birmingham, UK. She is also an International Federation of Colposcopy and Cervical Pathology certified colposcopist, a member of FOGSI and the AOGD Oncology committee, and web editor of ISCCP. She was clinical secretary of the Asia Oceania Association of Genital Infections and Neoplasia (AOGIN), India, and has conducted various cervical cancer prevention activities at the community level. She has delivered several lectures at national and international conferences and conducted colposcopy workshops. She has published three books and over 60 papers in respected national and international journals.

Contributors

Reshu Agarwal Department of Gynecologic Oncology, Prakhar cancer Centre, Kanpur, Uttar Pradesh, India

Sarfraz Ahmad, PhD Florida State University College of Medicine, Tallahassee, FL, USA

AdventHealth Gynecologic Oncology, AdventHealth Cancer Institute, Orlando, FL, USA

University of Central Florida College of Medicine, Orlando, FL, USA

Nidhi Arora Fetal Medicine, Madhukar Rainbow Children's Hospital, New Delhi, India

Manikankana Bandopadhyay, MSc, PhD Division of Molecular Genetics and Biochemistry, Indian Council of Medical Research (ICMR), National Institute of Cancer Prevention and Research, Noida, Uttar Pradesh, India

Ritisha Basu, MD Department of Obstetrics and Gynaecology, University College of Medical Sciencesand Guru Teg Bahadur Hospital, Delhi, India

Kanika Batra Modi Max Institute of Cancer Care, Max Hospital, Saket, New Delhi, India

Mausumi Bharadwaj, PhD, FNASc Division of Molecular Genetics and Biochemistry, Indian Council of Medical Research (ICMR), National Institute of Cancer Prevention and Research, Noida, Uttar Pradesh, India

Department of Health Research, Ministry of Health & Family Welfare, GOI, Noida, India

Shruti Bhatia, MD, DNB, MNAMS Department of Gyne Oncology, Action Cancer Hospital, Delhi, India

H. S. Darling, MD, DNB Narayana Superspeciality Hospital, Gurugram, Haryana, India

Emily Deibert, MD Florida State University College of Medicine, Tallahassee, FL, USA

Department of Obstetrics and Gynecology, Wake Forest School of Medicine, Winston-Salem, NC, USA

Heena Gautam, M Tech Division of Molecular Genetics and Biochemistry, Indian Council of Medical Research (ICMR), National Institute of Cancer Prevention and Research, Noida, Uttar Pradesh, India

Anshul Grover, DGO, DNB Department of Obstetrics & Gynecology, Babu Jagjivanram Memorial Hospital, New Delhi, India

Bindiya Gupta, MS, FICOG Obstetrics and Gynecology, UCMS & GTB Hospital, Delhi, India

Monisha Gupta Department of Gynecology Oncology, Max Institute of Cancer Care, Shalimar Bagh, Delhi, India

Sarika Gupta Gynecologic Oncology, Indraprastha Apollo Hospital, Delhi, India

Sunny Jandyal, MD, DM Department of Medical Oncology, Action Cancer Hospital, Delhi, India

Asmita Kaundal, MS, DNB, MNAMS Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India

Satinder Kaur, MD, DNB Gyne Oncology, Dharamshila Narayana Superspeciality Hospital, Delhi, India

Ritu Khatuja, DNB Department of Obstetrics & Gynecology, ANIIMS & G B Pant Hospital, Port Blair, Andaman & Nicobar Islands, India

Neha Kumar, MS, MCh Gynecologic Oncology, BLK Superspeciality Hospital, New Delhi, India

Abhishek Malakar, MS, DNB Department of Obstetrics & Gynecology, ANIIMS & G B Pant Hospital, Port Blair, Andaman & Nicobar Islands, India

Ankita Mann, MS Department of Obstetrics & Gynecology, Babu Jagjivan Ram Memorial Hospital, New Delhi, India

Sumita Mehta, DNB, FICOG Department of Obstetrics & Gynecology, Babu Jagjivan Ram Memorial Hospital, New Delhi, India

Thomas A. Paterniti, MA, MD Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta University, Augusta, GA, USA

Florida State University College of Medicine, Tallahassee, FL, USA

Anupama Rajanbabu Department of Gynecologic Oncology, Amrita Institute of Medical Sciences, Kochi, Kerala, India

Evan A. Schrader, MS, MD Florida State University College of Medicine, Tallahassee, FL, USA

Seema Singhal, MS, FACS, FCLS, MNAMS Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India

Anshuja Singla, DNB Department of Obstetrics and Gynaecology, University College of Medical Sciencesand Guru Teg Bahadur Hospital, Delhi, India

Kanika Sharma Sood Radiation Oncology, Dharamshila Narayana Superspeciality Hospital, New Delhi, India

Elizabeth A. Wilkinson, MD Florida State University College of Medicine, Tallahassee, FL, USA

Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville, FL, USA

Part I

Trends and Etiology of Endometrial Cancer

Changing Trends in the Epidemiology of Endometrial Cancer

1

Thomas A. Paterniti, Evan A. Schrader, Emily Deibert, Elizabeth A. Wilkinson, and Sarfraz Ahmad

1.1 Introduction

Uterine corpus cancer (UCC), alternatively referred to as endometrial cancer, is responsible for approximately 5% of the global cancer incidence and 2% of the global cancer mortality among women per year [1]. In 2012, UCC was the 6th most common cancer in women worldwide with an estimated 319,600 cases and was the 14th leading cause of cancer mortality, responsible for an estimated 76,200 deaths [1]. The incidence of UCC is highest in North America and Eastern Europe, and

T. A. Paterniti (✉)
Department of Obstetrics and Gynecology, Medical College of Georgia, Augusta University, Augusta, GA, USA

Florida State University College of Medicine, Tallahassee, FL, USA

E. A. Schrader
Florida State University College of Medicine, Tallahassee, FL, USA
e-mail: eas16d@med.fsu.edu

E. Deibert
Florida State University College of Medicine, Tallahassee, FL, USA

Department of Obstetrics and Gynecology, Wake Forest School of Medicine, Winston-Salem, NC, USA

E. A. Wilkinson
Florida State University College of Medicine, Tallahassee, FL, USA

Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville, FL, USA

S. Ahmad
Florida State University College of Medicine, Tallahassee, FL, USA

AdventHealth Gynecologic Oncology, AdventHealth Cancer Institute, Orlando, FL, USA

University of Central Florida College of Medicine, Orlando, FL, USA
e-mail: Sarfraz.Ahmad@AdventHealth.com

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_1

incidence rates coincide with several lifestyle factors common to higher-income countries, such as increased obesity, increased lifespan, later age of first childbirth, and fewer childbirths compared to lower-income countries [1]. The American Cancer Society (ACS) estimated that 167,900 new cases and 34,700 deaths would occur in more developed countries in 2012, compared to 151,700 new cases and <65,000 deaths in less developed countries [2]. Furthermore, women in more developed countries experience both a significantly higher lifetime risk of developing UCC (1.8% vs. 0.6%) and a higher cumulative mortality risk from it (0.3% vs. 0.2%) compared to those living in less developed countries [3].

Within the United States (U.S.), UCC is the fourth most common cancer diagnosed in females, accounting for 7% of all female malignancies, and the seventh most deadly, responsible for 5% of all cancer deaths in females [3, 4]. Fifty-three thousand nine hundred and eleven new cases of UCC were reported in 2015 (27 per 100,000) along with 10,733 UCC-related deaths (5 per 100,000) in 2016 [3]. The ACS estimated that 63,230 new cases of UCC would be diagnosed in the United States in 2018, resulting in 11,350 deaths [3, 4]. The incidence rate of UCC increased by 0.7% per year in 2015, while the death rate increased by 1.1% in 2016, with larger increases seen in ethnic minorities than in whites [3]. Overall, the incidence of UCC was higher among blacks and whites (27 per 100,000) than among other racial/ethnic groups (19–23 per 100,000); however, UCC-related deaths were highest among blacks (9 per 100,000) compared to all other racial/ethnic groups (4–5 per 100,000) [3]. The mean age at diagnosis for all types of UCC is 62 years, with 61% of cases diagnosed in women aged 55–74 years [5]. Among all women, 67% of UCC cases are diagnosed at an early stage due to postmenopausal bleeding, with 21% showing regional and 9% showing distant spread [3]. This distribution holds across all racial/ethnic groups except among blacks, where only 55% of UCC cases are localized at the time of diagnosis [3]. Of all cases of UCC, 68% are endometrioid carcinomas, while 24% are other carcinomas, 5% are carcinosarcomas, and 3% are sarcomas; in blacks, however, endometrioid carcinomas comprise only 47% of UCC cases, while 33% are other carcinomas, 12% are carcinosarcomas, and 7% are sarcomas [3].

UCC is typically treated with a combination of surgery, radiation, hormones, and/or chemotherapy, depending on the clinical picture [4]. The 5-year relative survival rate for all stages of UCC from 2007 to 2013 was 81%, and those with locally confined disease had a 5-year overall survival (OS) of 95%, compared to 69% in those with regionally confined disease and 16% in those with distant metastases [4]. The 5-year relative survival rate in all patients with UCC fell from 87% in 1975–1977 to 82% in 1987–1989, but has since remained relatively constant at 83% [4]. The median age at death due to UCC is 70 years, and nearly one-third of women who die from UCC are between the ages of 65 and 74 years [5]. UCC death rates vary among different races/ethnicities and were notably higher among blacks (9 per 100,000) in 2016 than among either whites (5 per 100,000) or those of other races/ethnicities (4 per 100,000) [3]. Between 1999 and 2016, UCC-related deaths increased approximately 21%, 1.1% per year on average, with larger increases seen among Asians/Pacific Islanders (A/PIs) (52%), Hispanics (33%), and blacks (29%) than occurred

in either whites (18%) or American Indians/Alaska Natives (AI/ANs, no significant increase) [3].

1.2 Type I and II Carcinomas

1.2.1 Pathophysiologic and Molecular Distinctions

Despite its varied clinical and histopathologic features, UCC was historically regarded as a single entity until Lauchlan, Hendrickson et al. differentiated uterine papillary serous carcinoma (UPSC) from endometrioid carcinoma, describing it as histologically similar to serous epithelial ovarian carcinoma [6, 7]. Bokhman was the first to classify UCC into two types, each demonstrating distinctive histologic, epidemiologic, and clinical features, which can be broadly characterized as estrogen-dependent and estrogen-independent [8, 9]. Type I carcinomas, referred to as "endometrioid," comprise 80–90% of all sporadic cases of UCC, are histologically adenocarcinomas, and are often well-differentiated [10]. Type II carcinomas, also referred to as "non-endometrioid," comprise the remaining 10–20% of UCC cases, and are made up of UPSC, clear cell carcinomas (CCC), as well as mucinous, squamous, transitional cell, mesonephric, and undifferentiated carcinomas [10]. Grade 3 (G3) endometrioid carcinomas are sometimes considered Type II carcinomas as well [11].

Type I carcinomas are broadly considered to be estrogen-dependent, with risk factors that coincide with chronic exposure to excess estrogen. These include obesity, estrogen-based hormone replacement therapy (HRT), nulliparity, as well as any medical condition resulting in elevated levels of estrogen, such as estrogen-secreting tumors or polycystic ovarian syndrome (PCOS) [10]. Associated comorbidities typically include hyperlipidemia, hypertension, and diabetes mellitus (DM) [8, 12]. Type II carcinomas, by contrast, are not thought to operate through a primarily estrogen-dependent pathway, and typically occur in older multiparous women of normal weight [8, 9]. One RCS (n = 396) found that 22% of UCC cases diagnosed in women >75 years were UPSC compared to only 3% in women <45 years [13]. The picture is not as simple as estrogen dependence versus estrogen independence, however, as a large prospective cohort study (PCS, n = 1,036,909) found that overweight and obese women were 1.26- and 1.94-times more likely, respectively, to develop Type II carcinomas than women of normal weight [14]. Furthermore, another PCS (n = 97,786) found that a body mass index (BMI) >30 kg/m^2 was significantly associated with Type II carcinomas [11]. It should be noted, however, that both studies grouped G3 endometrioid tumors with UPSC and CCC, which may explain the correlation, as other studies that did not group G3 tumors in this fashion showed an inverse relationship between BMI and Type II carcinomas [10]. At this point, it is safe to conclude that while increased BMI may be associated with both Type I and II carcinomas, it is more strongly associated with Type I carcinomas [10].

Advances in translational science have borne out the division of UCC into Type I and Type II carcinomas by demonstrating that variations seen histologically and

clinically correspond to differences in gene expression. In particular, *KRAS* and *PTEN* mutations are common in Type I carcinomas, as is epigenetic silencing of *MLH1*, resulting in microsatellite instability (MSI); these alterations occur with higher frequency in patients with hereditary nonpolyposis colorectal cancer (HNPCC) [15, 16]. Genomic abnormalities in chromosomes 1, 8, and 10 occur in both atypical hyperplasia and Type I carcinomas, and within 40% of histologically normal premenopausal endometrium there exist isolated glands that fail to express *PTEN*, either due to a mutation or a deletion; these glands persist between menstrual cycles, and with progression assume the appearance of atypical hyperplasia [15]. Other mutations that have been identified in Type I carcinomas include *PIK3CA*, *PIK3R1*, *FGFR2*, *ARID1A* (*BAF250a*), and *CTNNB1* (β-catenin) [16].

In contrast to Type I carcinomas, which are usually diploid, Type II carcinomas are typically aneuploid, and have their own characteristic profile of gene alterations [16]. For example, *TP53* (p53) mutations occur early and often in the development of UPSC, as do alterations of *PPP2R1A*, *PIK3CA*, and *PTEN* [15, 16]. Overexpression of human epidermal growth factor receptor 2 (HER-2/*neu*, also known as *cerbB2* or HER2) in UPSC has been demonstrated in smaller studies, and HER-2/*neu* overexpression has been associated with advanced-stage disease, worse progression-free survival (PFS), and worse OS, making it a possible marker of worse overall prognosis in UPSC [17–21]. Dysregulation or overexpression of aldolase C, desmoplakin, integrin-linked kinase (*ILK*), protein kinase C (*PKC*), *CLK,* p16, cyclin E, and *BAF250a* have also been reported in Type II carcinomas [15]. The genetic profile of CCC resembles that of UPSC; however, distinguishing specific mutations between histologic subtypes of Type II carcinomas is challenging due to their rarity and heterogeneity, and this represents a topic for further investigation [16].

1.2.2 Type II-Specific Epidemiologic Factors

Type II carcinomas have their own idiosyncratic epidemiologic features, which are discussed here in more detail. The remainder of this chapter, by contrast, focuses on the epidemiologic features of Type I carcinomas, since these are by far more prevalent. In particular, Type II carcinomas are more common in blacks, which may contribute to racial disparities in UCC survival [8–10]. An analysis of racial differences in four Gynecologic Oncology Group (GOG) chemotherapy trials found the incidence of UPSC to be 39% in blacks compared to only 16% in whites, with worse survival in blacks despite all groups receiving similar surgical and chemotherapeutic treatment [22]. However, disparities in survival were noted regardless of histologic subtype, suggesting that additional factors contribute to reduced survival in this cohort [22].

Overall, Type II carcinomas carry a significantly worse prognosis than Type I carcinomas, with 47% of UCC deaths occurring in Type II carcinomas despite these representing only 11% of diagnosed cases [10]. Furthermore, OS for Type I carcinomas is 83% compared to only 46–53% for UPSC and 42–63% for CCC [23–26]. The stage-adjusted OS is also significantly worse for Type II than for Type I

carcinomas, with Stage I UPSC having an OS of 50–80% compared to 80–90% in Stage I Type I carcinomas [25, 27–29]. There is conflicting data comparing survival between Stage I UPSC and Stage 1 G3 Type I carcinomas [9]. An analysis of the International Federation of Gynecology and Obstetrics (FIGO) data in 2001 (n = 473) found an equivalent OS between Stage I UPSC and Stage I G3 Type I carcinomas (72% vs. 76%); however, an analysis of the Surveillance, Epidemiology, and End Results (SEER) data from 1988 to 2001 (n = 3789) found a significant difference in 5-year disease-specific survival (DSS) between Stage I UPSC and Stage I G3 Type I carcinomas in both the early-stage (74% vs. 86%) and late-stage cohorts (33% vs. 54%) [27, 29].

Several factors contribute to worse outcomes in patients with Type II compared to those with Type I carcinomas. Type II carcinomas typically present in older patients, with a reported median age at diagnosis of 68 years for UPSC and 64–66 years for CCC, compared to a median age of 63 years for Type I carcinomas [23–26]. Furthermore, only 69% of patients with Type II carcinomas present with early-stage disease (Stage I-II) compared to 86% of patients with Type I carcinomas; notably, 41% of patients with UPSC and 33% of those with CCC present with late-stage disease (Stage III-IV) [24]. Type I carcinomas are typically minimally invasive, whereas Type II carcinomas tend to be deeply invasive, and in contrast to Type I carcinomas, which are more likely to recur locally and are frequently curable with tumor-directed radiotherapy, Type II carcinomas tend to recur distally, limiting the utility of radiotherapy in treatment [9].

Compared to those with Type I carcinomas, patients with Type II carcinomas are more likely to have a history of an additional primary cancer, with breast cancer being the most common, and in fact several retrospective studies have explored the association between breast cancer and UPSC [9, 10]. One retrospective cohort study (RCS, n = 592) noted the development of either a synchronous or subsequent breast cancer in 25% of patients with UPSC compared to only 3.2% of patients with Type I carcinomas, while another RCS (n = 1178) found a significantly higher likelihood of women ≤55 years with a history of breast cancer developing UPSC than Type I carcinoma, independent of Tamoxifen use [30, 31]. A third, smaller RCS (n = 54) found that women with breast cancer who later developed UCC were 2.6-times more likely to have UPSC than a Type I carcinoma, while an analysis of the SEER data from 1988 to 2001 (n = 52,109) found a significantly higher incidence of UPSC in women with a history of breast cancer than in those without it (9.4% vs. 6.3%) [30, 32].

Hypotheses for this phenomenon include similar shared risk profiles, the possibility of radiation therapy administered for one primary cancer inducing the other, both cancers being manifestations of an inherited cancer syndrome, such as HNPCC, or multiple cancers arising from mutations in unidentified cancer-predisposing genes [10]. Tamoxifen use has been proposed as contributing to the apparent association between UPSC and breast cancer; however, the evidence for this is conflicting, and the largest relevant study, a randomized controlled trial (RCT, n = 13,388), found no association between tamoxifen use and UPSC [9, 10]. A potential link between UPSC and hereditary breast–ovarian cancer syndromes is also

controversial, with some case series seeming to show an association between UPSC and *BRCA* mutations and others showing no connection [9, 33]. In the face of conflicting evidence, it has been suggested that mutations in as-yet-undescribed oncogenes may be responsible for observed associations between UPSC and breast cancer [9].

1.3 Age

The lifetime risk of developing UCC is 2.8% (1 in 35), and this risk steadily increases with age, from 0.3% (1 in 342) in women ≤49 years, to 0.6% (1 in 103) in women 60–69 years, to 1.3% in women ≥70 years [4]. The incidence of UCC in "young" women varies depending on the age cutoff used, but is reported to be 14.4% in women <40 years of age, 15% in women <45 years of age, and 12% in women <50 years of age [13, 34–36]. Compared to their older counterparts, younger patients with UCC are more likely to be obese, nulliparous, diabetic, hypertensive, to have polycystic ovaries, and to report a history of ovulatory dysfunction [34, 35]. Tumor grade and depth of myometrial invasion appear to increase with age, although it is uncertain whether this difference is due to progression of disease or simply to a later discovery [13, 24]. An analysis of FIGO data in 2006 ($n = 8807$) found that the mean age of patients with no myometrial invasion was 58.6 years, compared to a mean age of 61.5 years in patients with ≤50% myometrial invasion and 64.9 years in those with >50% myometrial invasion [24]. Younger patients with UCC are also more likely than their older counterparts to present with earlier-stage disease and with more favorable histologic subtypes, although approximately 25% present with Stage II-IV disease and 9% have positive lymph nodes at the time of diagnosis [34, 37]. Notably, this patient population is also more likely to have synchronous ovarian cancer, with a reported rate of 19% [36].

1.4 Race/Ethnicity

1.4.1 Blacks

Studies investigating the relationship between race/ethnicity and UCC risk in the United States have primarily focused on disparities between blacks and whites [38]. Although UCC has a slightly lower incidence among blacks than whites (26.5 vs. 27.0 per 100,000), blacks with UCC experience a significantly higher mortality rate than whites (9.0 vs. 4.6 deaths per 100,000), and survival is substantially lower for blacks at every stage of diagnosis [4, 38, 39]. An analysis of the SEER data from 1992 to 2008 that corrected for patients who had undergone hysterectomy showed an incidence of 136.0 per 100,000 among whites compared to 115.5 per 100,000 among blacks, a 73% and 90% increase, respectively, from the uncorrected totals [40]. The incidence rate increased more in blacks than in whites following this adjustment because blacks undergo hysterectomy more often than whites in the

United States for reasons that remain unclear [41]. From 2005 to 2014 the incidence of UCC increased 1% per year in whites and 2.5% per year in blacks [4]. Notably, the 5-year relative survival rate for UCC remains markedly lower in blacks than in whites (62% vs. 84%), while the death rate increased at a faster pace for blacks than for whites (2.1% vs. 1.5%) between 2006 and 2015 [4].

Overall, blacks are twice as likely to die from UCC as women from any other racial/ethnic group, and multiple factors appear to contribute to this increased mortality, including a higher incidence of aggressive histologic subtypes, idiosyncratic patterns of gene expression, failure to access quality healthcare services, failure to receive standard of care, and an increased incidence of comorbidities [3, 38, 39]. Multiple studies have found that blacks are more likely than whites to be diagnosed with late-stage disease and with more aggressive histologic subtypes [3, 4, 22, 42]. Parsing the impact of histopathologic from socioeconomic factors on UCC outcomes in blacks has been a focus of research for many years; however, relevant studies have yielded inconsistent and conflicting results on nearly every one of these topics.

Increased mortality as a result of more aggressive tumor types and later stage at diagnosis remains an attractive hypothesis to explain racial/ethnic disparities in UCC patients, as multiple studies have shown no significant association between race/ethnicity and outcomes in cohorts who receive similar treatment regimens once results are corrected for stage and histologic subtype [42, 43]. An RCS ($n = 984$) of patients with UCC at all stages found that blacks were much more likely to have Type II carcinomas than whites, including UPSC, carcinosarcoma, and leiomyosarcoma [43]. Blacks had an increased risk of death when all histologic subtypes were included; however, controlling for Type I versus Type II carcinomas revealed no difference in OS between any of the involved races/ethnicities [43]. Another RCS ($n = 766$) of patients with early-stage Type I carcinomas who were matched for stage and adjuvant treatment found that the 5-year recurrence-free survival (RFS) and disease-specific survival (DSS) were significantly lower in blacks than in whites; however, when results were adjusted for other prognostic factors, race/ethnicity was not found to be a significant predictor of outcomes [42]. Findings such as these would seem to indicate a histopathologic reason for racial disparities in UCC patients rather than a socioeconomic one.

Other studies, however, have yielded conflicting results. A retrospective analysis of four GOG trials ($n = 1151$) showed that the median OS in those with late-stage or recurrent UCC was worse among blacks than whites (10.6 vs. 12.2 months) despite the two receiving similar treatment regimens [22]. This disparity persisted even after adjustment for stage, histologic subtype, and grade 1–2 tumors; grade 3 tumors did not show a significant association between race/ethnicity and survival [22]. Racial/ethnic disparities were also seen in tumor responsiveness to therapy, with blacks less likely than whites to experience a complete or partial response to chemotherapy (34.9% vs. 43.2%), a finding that persisted across all four GOG trials [22]. It is uncertain whether these findings run counter to those cited previously, or whether they indicate the presence of specific racial/ethnic disparities in late-stage or recurrent disease that do not exist in early-stage and primary disease. It is

noteworthy, however, that despite representing approximately 30% of the U.S. population, Hispanics and blacks comprise less than 6% of all federally funded clinical trials, a reality which may in part account for the reduced effectiveness of standard treatment regimens in these populations [44].

Molecular differences in tumorigenesis have also been proposed as a potential etiology for racial/ethnic disparities in UCC patients; however, studies have failed to find consistent associations between mutations in single cancer-related genes and OS among racial/ethnic groups [45]. Mutations in the *PTEN* tumor suppressor gene and MSI are associated with favorable clinicopathologic features, *PTEN* mutations have been shown to be more common in whites with advanced disease, and this has been proposed as a reason for an improved prognosis in this cohort [45, 46]. However, in one case–control study (CCS, $n = 39$), *PTEN* mutations were not found to be predictive of improved outcomes after controlling for other clinicopathologic features, and a retrospective analysis ($n = 140$) of tissue samples from patients with late-stage disease showed that although MSI was associated with improved survival, there was no difference in MSI frequency between racial/ethnic cohorts [45, 46].

HER-2/*neu* represents a more promising target gene for elucidating racial/ethnic disparities in UCC, as HER-2/*neu* gene amplification in UPSC has been shown to occur more often in blacks than in whites and to be an important prognostic indicator for poor outcomes [18]. One CCS ($n = 30$) found that patients with UPSC and HER-2/*neu* gene amplification had a significantly shorter survival time from diagnosis to disease-related death compared to controls [18]. Other studies have investigated the role of p53, since its overexpression occurs in approximately 20% of UCC cases and is associated with a worse prognosis [45]. In one CCS ($n = 39$) blacks were seen to have a two- to threefold increased expression of mutant p53 compared to whites at all stages of UCC; however, increased expression of p53 as well as race/ethnicity were only found to be significant prognostic factors in late-stage disease [45]. Furthermore, this study used genome-wide characterization of gene expression in UCC and found it to be indistinguishable between blacks and whites, including the expression of p53, HER-2/*neu*, and *PTEN*, leading the authors to conclude that racial disparities in UCC outcomes cannot be accounted for by tumor-specific gene expression alone [45].

Several authors have documented an increased rate of medical comorbidities in blacks compared to whites, and this represents an attractive avenue for investigation, since conditions like obesity and DM may impact survival both directly by maintaining a more hospitable hormonal environment for tumorigenesis, as well as indirectly by rendering black patients poorer surgical candidates in the setting of a cancer whose primary therapeutic approach is surgical [12, 38]. One RCS ($n = 1144$) found that blacks with both Type I and Type II carcinomas had a higher median BMI than whites, and were twice as likely to have DM [12]. A clear connection between these comorbidities, race/ethnicity, and OS, however, has remained elusive, as DM in this study was associated with a worse OS in patients with Type I carcinomas, but no association was seen in Type II carcinomas, and race/ethnicity was not independently associated with OS in any group [12].

An older analysis of the SEER data from 1992 to 1998 (n = 21,561) found that blacks were significantly less likely to undergo surgery, even after adjustment for stage [47]. Among patients with Stage I UCC, 7.7% of blacks did not undergo surgery compared to only 2.2% of whites, whereas among patients with Stage II disease 20.8% of blacks did not undergo surgery compared to 6.0% of whites; adjusting for the use of surgery in this study reduced racial/ethnic disparities in survival somewhat, but not entirely [47]. The reasons for racial/ethnic disparities in surgical treatment have been shown to be multifactorial and complex, and may include reduced access to care, potentially discriminatory practices by surgeons or other health care organizations, differences in the extent of disease limiting the effectiveness of surgical therapy, and the presence of medical comorbidities making patients poorer surgical candidates [47]. One older CCS (n = 55,533) found that lower income was associated with a lack of treatment in blacks with Stage IV disease [48]. However, more recent studies have shown worse outcomes for blacks compared to whites despite equivalent treatment regimens, while other studies have demonstrated that patients of all races/ethnicities experience worse outcomes when not privately insured [22, 49]. For example, a large RCS (n = 228,511) found that patients of any racial/ethnic identity with advanced disease were less likely to receive standard-of-care postoperative radiotherapy or chemotherapy if they were insured by Medicare than if they had private insurance [49]. Furthermore, those with advanced disease experienced a worse survival if they were either uninsured or insured by Medicare or Medicaid than if they were privately insured [49]. Ultimately, although numerous studies have been conducted on health disparities between blacks and whites in the United States, a better understanding of the etiology of racial/ethnic disparities in UCC outcomes is still needed in order to provide targeted care to those at the highest risk for poor outcomes [39].

1.4.2 Hispanics

Although research into racial/ethnic disparities in UCC incidence and outcomes has historically focused on comparisons between blacks and whites, referred to in this section as non-Hispanic whites (NHWs), recent studies have begun exploring similar issues in more diverse racial/ethnic populations, including Hispanics, A/PIs, and AI/ANs. Hispanics represent the second largest racial/ethnic group in the United States after NHWs, and accounted for approximately 17.8% of the U.S. population in 2016, numbering 57.5 million [50]. The ACS estimates that there will be 6700 new cases of UCC in the Hispanic population in 2018, which will be responsible for 1000 deaths [50]. Hispanics are diagnosed with UCC at a lower rate than NHWs (23.2 vs. 27.0 per 100,000); however, UCC incidence among Hispanics continues to rise at a disproportionate rate compared to NHWs (1.8% vs. 0.5%) [3].

Several studies have shown that Hispanics are more likely to present at a younger age and with later-stage disease than NHWs; however, the existence of treatment and survival differences among Hispanics is more controversial [51]. Further complicating matters is the considerable variation that exists in defining study

populations, as some authors have investigated differences between Hispanics and NHWs, while others have focused on Hispanic Whites (HWs) versus NHWs, and still others have divided Hispanic populations by birthplace or ethnic origin, with resulting uncertainty as to how the findings of these investigations may be compared to one other. The "Hispanic Paradox" is a well-known phenomenon reported in several malignancies, in which Hispanics seemingly experience better outcomes than would be expected based on poor socioeconomic prognostic factors [50, 51]. Several explanations have been proposed for this phenomenon, including statistical limitations, a higher baseline life expectancy in Hispanic populations giving the appearance of an increased DSS, a younger age at presentation conferring a better prognosis, and logistical difficulties with follow-up and death ascertainment, especially in more fatal cancers that often lead to return migration following diagnosis ("salmon bias") [50, 51].

Several epidemiologic studies into racial/ethnic disparities among Hispanics have considered UCC of all types, while others have focused specifically on more aggressive histologic subtypes and higher-grade disease. An analysis of the SEER data from 2000 to 2010 ($n = 69{,}764$) found that Hispanics with UCC of all subtypes and stages presented at a younger age than NHWs, with a mean age of 58.0 years in U.S.-born Hispanics, 59.7 years in foreign-born Hispanics, and 56.5 years in Hispanics of unknown birthplace, compared to a mean age of 63.4 years in NHWs [52]. Hispanics were more likely to present with late-stage disease than NHWs (29.8% vs. 25.7%) and U.S.-born and foreign-born Hispanics were also more likely than NHWs to be diagnosed with a high-risk histology (4.8% and 5.9% vs. 3.9%) [52]. Hispanics of unknown birthplace, most of whom the authors hypothesized were naturalized HWs, had a significantly better OS than NHWs (91.6% vs. 86.5% in NHWs, 79.6% in U.S.-born Hispanics, and 78.4% in foreign-born Hispanics), and most of the survival disparity between Hispanics and NHWs was attributed to cancer characteristics such as stage and nodal status [52].

Investigations focusing on more aggressive subtypes of UCC have found that although Hispanics are more likely to be diagnosed with these varieties, they do not experience any difference in survival compared to NHWs [44, 53]. One large RCS ($n = 43{,}950$) found that like blacks, Hispanics with Type II and high-grade endometrioid carcinomas were more likely than NHWs to present with late-stage disease [53]. Hispanics in this study experienced improved all-cause survival compared to NHWs after controlling for treatment, comorbidities, and sociodemographic and histopathologic variables; however, a similar RCS ($n = 10{,}647$) found no difference in DSS between Hispanics and NHWs [44, 53]. Other authors have reported considerable heterogeneity in the incidence of G3 endometrioid carcinoma, carcinosarcoma, UPSC, and CCC among Hispanic subgroups, but have not found clear survival differences between these groups [54]. One RCS ($n = 26{,}416$) found that compared to NHWs, the overall incidence of Type II carcinomas was higher in blacks, Cubans, and Central and South Americans, but not in Mexicans or Puerto Ricans. Another large RCS ($n = 205{,}369$) found no difference in UCC-related mortality between different Hispanic subgroups [54, 55].

Other authors have focused on differences between HWs and NHWs, finding that although UCC incidence is lower among HWs than NHWs, UCC mortality is higher than would be expected among HWs based on its incidence [56, 57]. An analysis of the SEER data from 1988 to 2009 (n = 14,434) found that like other Hispanics, HWs are more likely to present at a younger age and with late-stage disease than NHWs; however, no difference in either OS or DSS was found after controlling for age, stage, histology, and treatment received [57]. No differences in clinicopathologic characteristics were seen between immigrant and native HWs; however, immigrant HWs had a better OS and DSS than native HWs [57]. A PCS (n = 3286) found that HWs were more likely to be diagnosed at a younger age and with late-stage disease than NHWs, but also found that HWs were more likely to have DM and hypertension, to live in rural low-income areas, and to have less education than NHWs [56]. Notably, this study found that controlling for either comorbidities or education completely eliminated the disparities seen in both DSS and OS for HWs compared to NHWs [56].

1.4.3 Asians/Pacific Islanders

Asian-Americans comprised 6.3% of the U.S. population in 2014, numbering approximately 20 million, and these along with Native Hawaiians and Pacific Islanders (collectively abbreviated A/PI), whose population is approximately 1.5 million, represent the most rapidly growing racial/ethnic group in the United States today [58]. The ACS estimates that there will be 2380 cases of UCC within the A/PI population in 2016, which will be responsible for 350 deaths [58]. A/PIs are diagnosed with UCC at a much lower rate than whites (19.2 vs. 27.0 per 100,000); however, an analysis of the SEER data from 1998 to 2009 (n = 105,083) found that they are more likely than whites to present at a younger age (57.7 vs. 64.3 years), with late-stage disease, and with either UPSC or CCC [3, 59].

Studies have yielded conflicting results on the impact of A/PI race/ethnicity on survival. One RCS (n = 1811) found that A/PIs were more likely to present with higher-grade tumors and less favorable histologic subtypes than whites, A/PIs had a significantly worse OS compared to whites, and A/PI race/ethnicity was found to be a poor prognostic factor on multivariate analysis [60]. Another RCS (n = 10,647), however, found no significant difference in DSS between A/PIs or Hispanics with high-grade endometrioid or Type II UCC compared to whites, and an analysis of the SEER data from 1988 to 2009 (n = 105,083) found that A/PIs had a significantly improved DSS and OS compared to whites, even after controlling for stage, histology, and treatment [44, 59]. A/PI immigrants were diagnosed at a younger age than their native counterparts (57.0 vs. 60.5 years) and were slightly more likely to have UPSC or CCC, although no more likely to present with late-stage disease [59]. A/PI immigrants had a significantly better DSS and OS than A/PI natives, but no differences were seen among A/PI subgroups (Chinese, Japanese, Filipino, Asian Indian/Pakistani) [59].

1.4.4 American Indians/Alaska Natives

There are approximately 5.2 million people in the United States who identify as American Indian and Alaska Native (AI/AN), accounting for 1.7% of the U.S. population [61]. AI/ANs are diagnosed with UCC at a lower rate than whites (23.1 vs. 27.0 per 100,000), and an analysis of the SEER data from 1988 to 2009 (n = 105,083) found a trend that did not quite reach significance for the diagnosis of AI/ANs at a younger age than whites (56.5 vs. 64.3 years) [3, 59]. AI/ANs were no more likely than whites to present with either late-stage disease or with UPSC or CCC, and they had no significant difference in DSS, but did experience a worse OS compared to whites after controlling for stage, histology, and treatment [59]. More investigation is needed to clarify epidemiologic trends in this population.

1.4.5 Global Trends

Cancer is a leading cause of female morbidity and mortality worldwide in both high-income countries (HIC) and in low- and middle-income countries (LMIC) because although women comprise approximately 49.5% of the global population, they represent a more significant proportion of the aging population due to differences in life expectancy and causes of mortality [1]. The cancer burden among women is expected to increase worldwide in conjunction with increasing life expectancy, an effect that is likely to be especially pronounced in LMIC due to changes in risk factors associated with economic development, which include increased rates of smoking, obesity, and physical inactivity, later age at first childbirth, and fewer childbirths [1].

UCC accounts for approximately 5% of the global cancer incidence and 2% of global cancer deaths among women [1]. It is the sixth most common cancer among females worldwide with an estimated 319,600 new cases in 2012 [1]. It is furthermore the fourth most common cancer in HIC with 167,900 estimated new cases in 2012 and an age-standardized ratio (ASR) of 14.7 new cases per 100,000 per year, and the seventh most common cancer in LMIC with 151,700 estimated new cases in 2012 and an ASR of 5.5 new cases per 100,000 per year [1, 2]. Excess body weight is estimated to account for approximately 34% of UCC cases worldwide, and incidence rates in the United States, Central and Eastern Europe, and in several other European countries (e.g., Norway, the United Kingdom, and Spain) have increased concomitantly with increases in average body weight since the year 2000 [1]. A trend toward later parity and decreased parity in rapidly developing countries has also led to increased UCC incidence in these regions [1].

UCC is the 14th leading cause of global cancer deaths among women with an estimated 76,200 deaths in 2012 and an ASR of 2.3 deaths per 100,000 per year in HIC, compared to 1.5 deaths per 100,000 per year in LMIC [1]. The highest rates of UCC incidence are seen in North America and Eastern Europe, while the highest mortality rates are seen in Melanesia, Eastern Europe, and the Caribbean [1]. Early diagnosis and treatment of UCC are common in HIC, where the 5-year survival is approximately 80%; in contrast, the 5-year survival remains substantially lower in

LMIC where women have more limited access to health care [1]. For example, the 5-year survival for UCC in Benghazi, Libya is only 17% [1].

1.5 Endogenous Estrogen Exposure

1.5.1 Pathophysiologic Mechanisms of Disease

The sections that follow discuss the epidemiologic risk factors for Type I carcinomas, which comprise roughly 80% of UCC cases; specific epidemiologic risk factors for Type II carcinomas are discussed separately above. Endometrioid adenocarcinoma is hypothesized to develop in the setting of prolonged estrogen exposure that is unopposed by a progestogen [62, 63]. According to this model, excess estrogen stimulates endometrial cell proliferation, thereby increasing the occurrence and subsequent accumulation of cellular mutations [62, 63]. This so-called "unopposed estrogen" hypothesis is primarily supported by epidemiologic data showing a significantly increased risk of UCC in users of estrogen-only oral contraceptive pills (OCPs) and HRT [64, 65]. It is also bolstered by laboratory findings demonstrating that endometrial cells are maximally stimulated in the presence of estrogen during the early follicular phase of the menstrual cycle and minimally stimulated in the presence of progesterone during the luteal phase [66]. The risk of administering unopposed estrogen in OCP and HRT regimens can be eliminated by adding progestogens for ≥10 days per month [67, 68].

Premenopausal women with syndromes of anovulation who also have progesterone deficiency are at increased risk of developing UCC, as are postmenopausal women with elevated circulating estrogen levels, and it has been hypothesized that the risk of endometrial neoplasia correlates in premenopausal women with progesterone deficiency, but in postmenopausal women with estrogen excess [69]. Although androgens do not have a direct stimulatory effect on endometrial cell proliferation, increased levels of circulating androgens are believed to increase UCC risk in postmenopausal women due to aromatization in peripheral tissues (especially adipose tissue) once ovarian production of estrogen ceases [69, 70]. Thus, obesity in postmenopausal women increases circulating levels of estrogen via increased aromatization in peripheral tissues, whereas its effects in premenopausal women are primarily caused by ovulatory cycles and associated progesterone insufficiency [70]. Androstenedione levels also strongly correlate with UCC risk, even when estrone levels are controlled for, leading to the hypothesis that early neoplastic endometrial cells may have the ability to aromatize androstenedione locally, resulting in a survival advantage [70].

1.5.2 Chronic Anovulation

Women with ovulatory dysfunction continue to produce sex hormones, but do not produce them cyclically [71]. Chronic anovulation in this setting results in prolonged exposure to estrogens without concomitant exposure to progesterone,

leading to chronic endometrial proliferation, irregular bleeding, endometrial hyperplasia, and eventually carcinoma [71]. Anovulation may be physiologic at the outset of both menarche and menopause, whereas the causes of pathologic ovulatory dysfunction are many and varied, encompassing primary hypothalamic–pituitary dysfunction, acquired endocrine disorders, and medication side effects [71]. Polycystic ovary syndrome (PCOS) is a common endocrine and multisystem disorder affecting approximately 5–8% of reproductive-aged women [71]. It classically presents with a triad of symptoms that includes hyperandrogenism, menstrual abnormalities, and polycystic ovaries, with commonly associated comorbidities including insulin resistance and the metabolic syndrome [71]. A potential association between PCOS and UCC was first described in the 1950s; however, this risk is still frequently overlooked in clinical practice [71]. One PCS (n = 40,775) found a significantly higher risk of UCC in patients with PCOS than in the comparison cohort, and a recent meta-analysis (n = 72,973) found that PCOS increased the risk of UCC in women of all ages, with this risk even more pronounced in women ≤54 years [71, 72]. Another large PCS (n = 3,493,604) similarly found that PCOS was associated with an increased risk of UCC; however, this increased risk was only present before menopause [73].

1.5.3 Obesity

UCC was the first cancer to be recognized as causally related to obesity, and increasing rates of UCC in Western cultures, which are now approximately 10 times higher than elsewhere, have paralleled increasing rates of obesity [74]. Recent estimates suggest that up to 90% of all UCC cases are to some degree attributable to obesity, and the relative risk (RR) of both developing UCC (RR 7.1) and of dying from it (RR 6.25) is higher for patients with a BMI >40 kg/m^2 than it is for any other obesity-driven cancer [74–76]. UCC arises in the context of prolonged exposure to increased levels of bioavailable estrogen, with obesity contributing to this state in two primary ways: first, adipocytes may directly increase estrogen levels by converting either testosterone, androstenedione, or estrone to estradiol via aromatase; second, insulin resistance, which often accompanies obesity, may lead to decreased levels of sex hormone binding globulin (SHBG), increasing estradiol levels indirectly [74, 77, 78]. Excess levels of estrogen may also lead to chronic progesterone deficiency and chronic inflammation, resulting in continuous endometrial cell proliferation with decreased apoptosis and increased angiogenesis [77, 79]. In contrast to other disorders linked to obesity, the risk of developing UCC is associated with the amount of adipose tissue rather than its distribution [80, 81].

Studies have consistently shown a strong correlation between obesity and UCC risk. One meta-analysis (n = 3,044,538) reported that a 5 kg/m^2 increase in BMI significantly increased UCC risk (RR 1.59), while two large PCSs (n = 495,477, n = 62,573) found a consistent increase in risk as BMI rose above 25 kg/m^2, up to a RR of 4.50 for a BMI >30 kg/m^2 and 6.25 for a BMI ≥40 kg/m^2 [75, 82, 83]. Obesity is particularly associated with an increased risk of UCC in pre- and peri-menopausal

women, who comprise approximately 25% of all cases [74]. Two RCSs (n = 38, n = 188) found that 61% of UCC patients <40 years, 71% of those <45 years, and 56% of those <50 years had a BMI >30 kg/m^2 [36]. Interestingly, UCC risk was also increased in those with a BMI >25 kg/m^2 at 20 years of age and in those whose BMI had increased by 8 kg/m^2 since age 20 (RR 2.38) [83]. Another large PCS (n = 50,376) similarly found associations between weight at a young age, the magnitude of weight gained, and UCC risk, reporting that women with a 1% annual increase in BMI had a 3.2-fold increased UCC risk compared to those who had maintained a stable BMI. This study also found that a 35% increase in BMI conferred significant additional risk of developing UCC (RR 4.12) [84].

Elevated BMI has been shown to increase the risk of both Type I and Type II carcinomas, with the greatest effect seen on Type I disease [10, 85]. One RCS (n = 1411) found that patients with Type I carcinomas were more likely than those with Type II carcinomas to be obese (66% vs. 51%); however, grouping overweight and obese patients together mitigated this difference somewhat (85% vs. 79%) [12]. Several studies have also explored the role of obesity in the stage and tumor grade of UCC at the time of diagnosis. One RCS (n = 396) found that a BMI ≥40 kg/m^2 was associated with endometrioid histology and G1 disease, and other studies have similarly reported obesity-related risk to be higher in less aggressive forms of UCC [37, 86]. Larger and more recent studies that focused solely on endometrioid tumors, however, have found no association between obesity and either stage or tumor grade at the time of diagnosis [87, 88]. Obesity may impact the prognosis of UCC either directly through tumor-associated factors or indirectly via the role of associated comorbidities; however, the magnitude of its impact on survival remains uncertain. One RCS (n = 1411) found that increased BMI was associated with a shorter time to recurrence in Type I carcinomas, but no clear association was seen between BMI and OS for any histopathologic type, tumor grade, or stage [12]. Obese UCC patients have been shown to experience worse outcomes following treatment, and are more likely to die of both their comorbidities and their cancers than their counterparts with a BMI <25 kg/m^2 [74].

The incidence of obesity in the United States is highest among blacks and Hispanics for every age group above 20 years [89]; however, UCC incidence remains highest among whites [85]. One PCS (n = 47,557) found that among blacks, obesity at 18 years of age and amount of weight gained since that time were both associated with an increased risk of UCC [90]. Comorbid Type 2 DM was also associated with increased UCC risk, although positive associations with hypertension and weight distribution were attenuated after controlling for BMI [90]. The interplay between race/ethnicity and obesity on UCC risk remains controversial. One PCS (n = 46,933) of postmenopausal blacks, A/PIs, Hispanics, and whites found the risk of UCC to be similarly increased in women of all races/ethnicities with a BMI >30 kg/m^2 (RR 3.14), and the authors concluded that differences in comorbidities such as obesity did not sufficiently account for differences in UCC risk between these racial/ethnic groups [85]. However, another large PCS (n = 50,376) did find that increases in UCC risk differed across racial/ethnic groups, with only a ≥5% increase in BMI needed to increase UCC risk in Japanese-Americans, compared to a ≥35% increase needed in blacks and whites [84].

1.5.4 Early Menarche and Late Menopause

According to the "unopposed estrogen" theory of endometrial carcinogenesis, any menstrual factors prolonging the duration of estrogen exposure (e.g., early age at menarche, late age at menopause, and nulliparity) are predicted to increase the risk of UCC, while factors shortening or interrupting such exposure (e.g., pregnancy) are predicted to confer a protective effect. Two large prospective cohort studies support these hypotheses: one (n = 24,848) found that UCC occurrence was associated with early age at menarche, late age at menopause, and total length of ovulation span, while another (n = 121,700) found that late age at menarche decreased the risk of UCC, whereas late age at menopause increased it [91, 92].

1.5.5 Estrogen-Secreting Tumors

Ovarian tumors that produce estrogen or its precursor androstenedione may lead to the development of UCC. Sex cord-stromal tumors (SCSTs) are rare neoplasms arising from the ovarian stroma that account for approximately 3–5% of all ovarian malignancies [93]. These are composed primarily of granulosa cell tumors (GCTs), which secrete estradiol, and theca cell tumors/thecomas (TCTs), which secrete androstenedione [94, 95]. Prolonged exposure to tumor-derived estradiol from either tumor type may result in glandular or atypical adenomatous hyperplasia, adenocarcinoma in situ, or invasive carcinoma [95]. Endometrial hyperplasia has been reported in 27% of patients with SCSTs, whereas endometrial adenocarcinoma has been reported in 5–10% of patients with GCTs, and may be its presenting sign [93, 95]. A clinicopathologic review that distinguished 118 GCTs from 82 TCTs found that adenocarcinoma was more prevalent in patients with TCTs (26.8% vs. 12.2%), whereas endometrial hyperplasia was more common in patients with GCTs (55.3% vs. 36.6%) [96]. This same study reported a 66% incidence of hyperplasia or malignancy among all participants, with this combined incidence nearly equal between tumor types [96]. Women who develop SCST-associated endometrial carcinoma usually have well-differentiated, early-stage tumors that carry a good prognosis [95].

1.6 Exogenous Estrogen Exposure

1.6.1 Unopposed Estrogen Therapy

Multiple studies have suggested a causal relationship between the use of "unopposed" estrogen therapy (the administration of estrogen without the addition of a progestogen) and the development of endometrial hyperplasia and subsequent carcinoma [67]. Endometrial hyperplasia is a known precursor to the development of UCC, and thus its presence is often used as an endpoint in prospective trials for patient safety. One RCT (n = 1724) found that 20% of postmenopausal women

taking estrogen alone developed endometrial hyperplasia compared to ≤1% of those also taking a progestogen [97]. It was historically debated whether the use of cyclical unopposed estrogen might be safer than continuous administration, since this regimen was seen as more closely mimicking the natural estrus cycle; however, an RCT ($n = 25$) of postmenopausal women found a 36% rate of endometrial hyperplasia in users of unopposed estrogen with no difference seen between continuous and cyclical administration [97]. Case–control studies have reported a RR of developing UCC as high as 12.0 in ever-users of unopposed estrogen therapy, and up to 15.0 in long-term users, whereas a PCS (n = 23,244) reported a RR of 1.8 following >6 years of use, with cyclical addition of progestogens eliminating this increased risk [98, 99]. Finally, a Cochrane review found that unopposed estrogen therapy at all doses was associated with a significantly increased risk of endometrial hyperplasia following 2–3 years of use compared to placebo, with evidence of both a dose–response and a duration-of-treatment–response relationship, although endometrial hyperplasia was not seen following only 1 year of low-dose estrogen use [67].

It is less certain what impact unopposed estrogen use has on the aggressiveness of cancers that arise as a result of it. One older CCS (n = 363) reported that UCC occurring in users of unopposed estrogen was more likely to present at an earlier stage, with better differentiation, and with less myometrial invasion that UCC arising in nonusers [100]. This study further reported a better 4-year relative survival ratio in unopposed estrogen users than in nonusers (1.05 vs. 0.898), suggesting a better prognosis for UCC arising in this setting [100]. Other studies, however, have found opposite results. A CCS (n = 1217) found that in addition to increasing the risk of early-stage disease, the use of unopposed estrogen for >1 year also increased the risk of late-stage UCC threefold [101]. Additionally, women with ≥1 year of unopposed estrogen use remained at increased risk for at least 10 years following cessation of use [101]. Apparent improvements in survival among estrogen users in some studies may reflect increased access to health care and increased disease surveillance, with a resultant lead time bias [100].

1.6.2 Postmenopausal Hormone Replacement Therapy

Progestogens decrease the proliferation of endometrial glandular cells by down-regulating estrogen receptors, mediating the metabolic inactivation of estradiol, and reducing DNA synthesis [102]. Consequently, several large prospective studies have found that the addition of progestogens to estrogen significantly reduces the risk of developing endometrial hyperplasia and carcinoma compared to the use of estrogen alone [67]. One large RCT (n = 16,608) found that 62.2% of postmenopausal women given unopposed estrogen developed some type of endometrial hyperplasia with 34.4% developing complex hyperplasia or atypia [103]. Overall, these women were more likely than those taking placebo to develop simple (27.7% vs. 0.8%), complex (22.7% vs. 0.8%), or atypical (11.8% vs. 0%) hyperplasia as their most abnormal diagnosis [103]. Those taking continuous estrogen–progestogen therapy did require more frequent endometrial biopsies to assess vaginal

bleeding than those taking placebo (33% vs. 6%); however, they did not experience an increase in the rate of either hyperplasia or UCC [103]. Another large PCS (n = 716,738) found that the RR of UCC was increased with the use of estrogen alone (RR 1.45), but not significantly increased with the addition of a cyclical progestogen (RR 1.05), and in fact decreased with the addition of a continuous progestogen (RR 0.70) [104].

Some studies have reported BMI to be an effect modifier, such that the adverse effects of unopposed estrogen were greatest in nonobese women, while the beneficial effects of combined estrogen–progestogen therapy were greatest in obese women, but other studies have failed to confirm this finding [102, 104–106]. Several studies have attempted to quantify both the optimum monthly duration of progestogen use needed to maximize its protective effect and to determine whether cyclical regimens confer the same protection as continuous administration. One CCS (n = 340) found an increased risk of UCC with <10 days of progestogen use per month compared to ≥10 days (RR 2.4 vs. 1.1) of progestogen use. Similarly, another CCS (n = 1624) found that whereas the addition of a sequential progestogen for <10 days per month only slightly reduced the risk of developing UCC compared to the use of unopposed estrogen (odds ratio [OR] 1.87 vs. 2.17), the addition of a continuous oral sequential progestogen for ≥10 days essentially eliminated this risk (OR 1.07 for both) [68, 107].

Two high-quality prospective studies have yielded conflicting results regarding the benefits of cyclical progestogen use compared to continuous administration. One PCS (n = 224,015) found a significant risk reduction among users of continuous estrogen–progestogen therapy for ≥3 years compared to sequential use for 10–14 days per month (76% vs. 69%), and reported a 276% increased risk when progestogens were only added every 3 months (a so-called "long-cycle regimen") [108]. By contrast, a Cochrane review that examined sequential combined therapy with regimens of 10, 12, and 14 days of a progestogen per monthly cycle, as well as an alternating 3-days-on-3-days-off regimen throughout the cycle, found no increased odds of endometrial hyperplasia or carcinoma at 12, 24, or 36 months with any of these regimens compared to continuous progestogen administration [67]. Several RCTs have assessed the impact of various doses of estrogen and progestogens administered in both continuous and cyclical fashion, with no differences seen in the rates of either endometrial hyperplasia or carcinoma between any of the dosages delivered continuously [67]. The only RCT to find a significant increase in endometrial hyperplasia with cyclical progestogen administration utilized a long-cycle regimen [67].

1.6.3 Tamoxifen, Other SERMs, and Aromatase Inhibitors

Selective estrogen-receptor modifiers (SERMs) are nonsteroidal compounds with dual estrogen-agonist and antagonist activity on estrogen receptors in different tissues [109]. Commonly prescribed SERMs include tamoxifen, which is primarily used in the treatment of ER-positive breast cancer; raloxifene; which is indicated for the treatment of osteoporosis; and toremifene, which is approved for the treatment

of advanced breast cancer [109]. Multiple large RCTs have demonstrated significant increases in the risk of endometrial hyperplasia and carcinoma with tamoxifen use, and this risk has been found to be age-dependent, dose-dependent, duration-of-treatment-dependent, and persisting for extended periods of time following cessation of use [110, 111]. One RCT (n = 1846) found that the frequency of UCC was markedly higher in those given tamoxifen compared to placebo (RR 6.4), although this increase did not reach significance until two years of use, and the greatest increased risk was seen in patients allocated to five years of tamoxifen therapy [112]. Another large RCT (n = 13,388) found that women randomly assigned to receive five years of tamoxifen experienced a significantly elevated risk of UCC (RR 3.28) compared to placebo [113]. Although this risk was not increased in women <49 years, it was significantly increased in those ≥50 years (RR 5.33), with the highest cumulative rate of UCC seen in those with seven years of tamoxifen use compared to placebo (15.64 vs. 4.68 per 1000) [113].

The risk of UCC in young patients (<50) is of particular interest as tamoxifen has shown utility in the prevention of breast cancer in young patients at high risk, notably in those who have developed contralateral breast cancer previously and in those with *BRCA1* or *BRCA2* mutations [114]. One meta-analysis (n = 21,457) found that women who received approximately five years of tamoxifen therapy had an overall increased risk of developing UCC (rate ratio 2.40), with the effects of tamoxifen persisting long after cessation of use [115]. However, the 15-year risk of UCC was strongly correlated with age, with little absolute risk in patients with an entry age of <55 years compared to a much greater risk in those with an entry age of 55–69 years (3.8% vs. 1.1%); the sample size for an entry age ≥70 was too small for a comparison to be made [115]. These results were strengthened by a systematic review of seven RCTs, including data from the NSABP P-1, IBIS-1, and Royal Marsden trials, which found the RR of UCC to be 1.18 in women <50 years given tamoxifen compared to placebo [111].

Several studies have investigated whether UCC arising in the setting of tamoxifen use carries a significantly different prognosis than cases arising sporadically. Early case series reported conflicting results, with more recent case–control and cohort studies doing little to resolve this issue [112, 116]. One CCS (n = 1169) found that tamoxifen use in patients with UCC following breast cancer was associated with a higher-than-expected incidence of late-stage disease (17.4% vs. 5.4%), and tamoxifen users were found to have a worse 3-year DSS than nonusers (76% for use ≥5 years, 85% for use of 2–5 years vs. 94% for nonusers) [117]. Furthermore, long-term tamoxifen users in this study were found to be more likely than nonusers to develop malignant mixed mesodermal tumors (MMMTs) or sarcomas (15.4% vs. 2.9%) and p53-positive tumors (31.4% vs. 18.2%), associations which have been alluded to in numerous case reports [110, 117]. On the other hand, an RCS (n = 73) of patients with a history of breast cancer who subsequently developed UCC found no significant difference in stage, tumor grade, or histologic subtype between those given tamoxifen and those who did not receive it [118]. Numerous studies and case reports have been published on this topic; however, these are of significant heterogeneity and quality, and more investigation is needed [110].

Great uncertainty remains regarding the utility of either oral, transdermal, or intrauterine progestogens in counteracting the proliferative effects of tamoxifen. A Cochrane review of two studies investigating the use of a levonorgestrel-releasing intrauterine device (LNG-IUD) was inconclusive, as neither of the studies under consideration were sufficiently powered to detect the device's ability to prevent either endometrial hyperplasia or carcinoma in tamoxifen users [119]. Likewise, it is unknown whether administering progestogens in any form decreases the risk of UCC in tamoxifen users, and their use for this purpose is not currently recommended [120].

Unlike estrogen and tamoxifen, raloxifene acts as an antagonist on estrogen receptors in the endometrium, and thus its use would not be predicted to increase the risk of developing UCC [114]. Two studies have largely confirmed this hypothesis. One, a CCS (n = 1957), reported a reduced risk of UCC in patients treated with raloxifene compared to those given tamoxifen or placebo (OR 0.50 vs. 1.5 vs. 1.0), and found that endometrial carcinomas arising in raloxifene users were predominantly associated with a favorable stage, tumor grade, and histologic subtype. The second, an RCT (n = 7705), found that although raloxifene led to slight increases in endometrial thickness in some patients compared to placebo, no increased risk of endometrial hyperplasia was seen within the first 3 years of use [114, 121].

Aromatase inhibitors (AIs) are a class of drugs that include exemestane, letrozole, and anastrozole, and which are used in the treatment of breast cancer, endometriosis, for induction of ovulation, and in other estrogen-modulated conditions [122]. Studies have consistently shown a decreased risk of UCC in patients using AIs compared to those using tamoxifen; however, this benefit must be weighed against various other factors, including increased bone loss due to AIs and overall considerations of effectiveness in the treatment and prevention of breast cancer [122]. A large RCS (n = 17,064) of women diagnosed with ER-positive breast cancer found a 48% lower incidence of UCC in patients assigned to AIs compared to those given tamoxifen; no difference in UCC incidence was seen between those using AIs and those given no adjuvant hormonal therapy [123]. One meta-analysis of nine RCTs (n = 31,920) found a 30% decreased 10-year incidence of UCC in those randomized to AIs compared to those given tamoxifen (0.4% vs. 1.2%, rate-ratio 0.33), while another systematic review and meta-analysis (n = 30,023) found that five years of AI use decreased the risk of UCC compared to the same duration of tamoxifen use (OR 0.34) [115, 124].

1.7 Genetic Syndromes

1.7.1 Family History

An estimated 5% of patients diagnosed with UCC at <55 years report a positive family history, and woman with at least one first-degree relative affected by UCC have an increased lifetime risk of developing it themselves compared to the general population (3.1% vs. 1.7%) [125, 126]. No evidence has been found for an increased

risk of Type I carcinoma in women with a first-degree family history of breast, ovarian, or cervical cancer; however, one study reported an increased risk of Type II carcinoma in those with a first-degree family history of breast cancer [126]. Epidemiologic studies have shown an association between UCC and colorectal cancer, likely due to the fact that UCC is the most common extracolonic malignancy arising in Hereditary Nonpolyposis Colorectal Cancer (HNPCC), a syndrome associated with a DNA mismatch repair (MMR) deficiency [125]. Patients occasionally present with UCC alone without colorectal or other cancers, and investigators have recently attempted to define a unique etiology for these so-called "site-specific" cases [125]. Both pedigree and molecular analyses strongly suggest an origin for some cases of UCC that is unrelated to an MMR defect; however, the identity of the specific genes responsible remains elusive [125, 127].

1.7.2 Hereditary Nonpolyposis Colorectal Cancer (Lynch Syndrome)

Hereditary Nonpolyposis Colorectal Cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant disorder characterized by an increased susceptibility to colorectal, endometrial, and several other cancers [128]. HNPCC is caused by defects in the MMR genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, which result in variably sized nucleotide repeats throughout the genome, a phenomenon known as microsatellite instability (MSI) [128, 129]. High levels of MSI may be caused by either inherited HNPCC-associated genes or they may result from sporadic or non-hereditary MMR gene silencing via DNA methylation, a phenomenon estimated to occur in 15–20% of sporadic UCC cases [129]. A cross-sectional study (n = 58) found that of those with both UCC and a positive first-degree family history of HNPCC, 23% had an MMR gene mutation [128]. Compared to a 3% risk in the general population, the cumulative lifetime risk of developing UCC in those with HNPCC is 40–60%, with a reported risk of 25–42% for *MLH1* carriers, 35–62% for *MSH2* carriers, and 71% for *MSH6* carriers [128–132]. No significant difference in UCC risk has been found between *MLH1* and *MSH2* carriers [131].

Those with HNPCC may have a higher lifetime risk of developing UCC than colorectal cancer, and UCC in many patients represents a sentinel cancer, often diagnosed at an earlier age than colorectal cancer [133]. One cross-sectional study (n = 117) found that 44% of HNPCC patients with metachronous primary cancers were diagnosed with UCC as their first cancer, and 51.5% were diagnosed with a gynecologic cancer (UCC or ovarian cancer) first compared to 48.5% diagnosed with colorectal cancer first [130]. Within this cohort, the median age at the diagnosis was slightly greater for those developing UCC first compared to those developing colorectal cancer first (45 vs. 40 years) [130]. Compared to the general population, women with HNPCC are diagnosed with UCC at a much younger age (48 vs. 63 years), with 57% of cases diagnosed at <50 years and 98% of cases diagnosed at <65 years [128, 129]. The mean age at the diagnosis of UCC is not significantly different for carriers of an *MLH1* or *MSH2* mutation compared to the overall

HNPCC population, although UCC may be diagnosed at an older age in *MSH6* carriers [128]. There is no data to suggest a worse disease-specific prognosis for women with HNPCC-associated UCC compared to those who develop it sporadically [129]. It is uncertain whether cases with elevated levels of MSI (so-called "MSI-high" cases) result in a worse prognosis, as investigations into this issue have reported mixed results [129].

1.7.3 Cowden Syndrome

Cowden syndrome (CS) is an autosomal dominant disorder characterized by benign hamartomas and an increased risk for breast, thyroid, endometrial, and other cancers [134]. CS is one of several syndromes associated with *PTEN* mutations, and the presence of UCC was recently added as a major criterion in the revised International Cowden Consortium Diagnostic criteria for CS [135]. Larger case–control studies have reported a 12.5–19% lifetime risk of UCC in CS patients, with a cumulative risk of 1% at age 40, 9% at age 50, and 19% at age 60 [134, 136]. The estimated screening age needed to capture 95% and 100% of UCC cases in this population is 32 and 22 years, respectively [134].

1.7.4 *BRCA1* and *BRCA2* Mutations

Inherited mutations in the *BRCA1* and *BRCA2* genes are widely known to confer a greatly increased risk of breast and ovarian cancer, as well as a smaller, but still significantly increased, risk of several other cancers [31]. Papillary serous carcinoma is the most common histologic subtype of *BRCA* mutation-associated ovarian cancer and UPSC has a known association with breast cancer. Both of these facts have led to speculation that a *BRCA* mutation may increase the risk of developing UCC. Several smaller case reports and retrospective studies have explored these associations with suggestive findings; however, larger retrospective studies have produced conflicting results [33, 137]. One epidemiologic study and two RCSs found no increased incidence of *BRCA* mutations in Ashkenazi Jewish patients with UCC compared to the Ashkenazi Jewish population as a whole, and the authors concluded that UPSC is not a manifestation of any known hereditary breast–ovarian cancer syndrome, that *BRCA* mutations do not predispose to UPSC, and that the observed association between UPSC and breast cancer is likely due to mutations in as-yet-unknown cancer-predisposing genes [9, 31, 33, 138]. Another large RCS (n = 11,847), however, found a significantly elevated risk of UCC in those with a *BRCA1* mutation (RR 2.26) [139]. Two large PCSs have similarly produced conflicting results, with one (n = 857) finding no increased risk of UCC in women who had not previously used tamoxifen, but another (n = 1083) concluding that although the overall risk for UCC was not higher in *BRCA* carriers compared to the general population, the risk for serous/serous-like endometrial carcinoma was increased in those with a *BRCA1* mutation [140, 141]. Further investigation is needed to clarify

this issue, as findings would have relevant clinical implications for both screening and risk-reduction surgery in patients with *BRCA* mutations.

1.8 Fertility-Associated Factors

1.8.1 Nulliparity and Infertility

Parity is protective against UCC, likely due to the effects of progesterone produced to support the pregnancy, and infertile women may be at increased risk for UCC independent of parity, particularly if their infertility is the result of ovulatory dysfunction [142, 143]. PCOS, the most common ovulatory disorder, is accompanied by several risk factors for UCC, such as chronic anovulation, obesity, and hyperinsulinemia, and is discussed in more detail above. A large meta-analysis ($n = 69{,}681$) found an inverse association between parity and UCC risk with a nonlinear dose–response relationship, while an umbrella review of 171 meta-analyses reported a 40% reduction in UCC incidence among parous compared to nulliparous women [143, 144].

Two large studies have shown a reduction in UCC risk with increasing age at last pregnancy; however, the mechanism responsible for this finding remains unclear [143]. A large PCS ($n = 121{,}700$) as well as a pooled analysis of retrospective data ($n = 25{,}233$) found that women who had birthed their last child at age ≥40 years were at a 44–49% decreased risk of developing UCC compared to those who birthed their last child at age ≤29 years [91, 145]. This association was seen in both Type I and Type II carcinomas, and no effect modification was observed from BMI, parity, or exogenous hormone use [145]. The impact of incomplete pregnancy remains unclear. A large PCS ($n = 24{,}848$) found an association between UCC risk and a history of either an induced abortion or a miscarriage late in reproductive life, and the authors hypothesized that the latter scenario may be indicative of progesterone deficiency [92]. A smaller CCS ($n = 1666$), on the other hand, found that both completed and aborted pregnancies were protective against UCC, while another CCS ($n = 702$) concluded that both spontaneous and induced abortions were unrelated to UCC risk [146, 147].

The known protective effect of nulliparity has generated investigations into the impact of infertility treatments on UCC risk, especially since clomiphene citrate, a SERM used for ovulation induction, increases estradiol levels through a mechanism comparable to tamoxifen, which is widely known to increase the risk of UCC [148, 149]. One RCS ($n = 8431$) concluded that ovulation induction with clomiphene citrate increases UCC risk twofold, particularly in larger doses and when given for a longer period of time [148]. Notably, this risk was increased more than threefold in nulligravid women, sixfold in obese women, and more than twelvefold in women who were both nulligravid and obese compared to untreated infertile women [148]. A latency effect was also seen in this study (≥20-years), suggesting that the failure of other studies to find a significant association may be due to shorter follow-up periods [148]. Another large RCS ($n = 20{,}656$) found that UCC

was more common than expected in women with unexplained infertility, irrespective of their *in vitro* fertilization (IVF) status; however, no higher incidence of UCC was seen in women exposed to fertility drugs compared to those unexposed [150]. Currently, the relationship between infertility therapy and UCC risk apart from other accompanying risk factors for infertility (e.g., chronic anovulation and obesity) remains unclear.

1.8.2 Breastfeeding

Breastfeeding has long been suspected to impact the risk of developing UCC due to accompanying hormonal changes, since exclusive breastfeeding suppresses ovulation and thereby decreases maternal estrogen levels [151]. Several epidemiologic studies have investigated this association, however with mixed results [152]. A recent meta-analysis (n = 623,570) concluded that each month of breastfeeding decreases UCC risk by 1.2%, even after controlling for both hormone use and BMI, while another meta-analysis (n = 26,222) reported an 11% UCC risk reduction in those who had ever breastfed, even after controlling for parity, BMI, and tumor histology [151, 152]. Longer durations of breastfeeding decreased the risk of developing UCC in a dose–response relationship, although the effect appeared to level off beyond 6–9 months [151].

1.8.3 Contraceptives

More than 300 million women have used OCPs since their introduction in the 1960s, and an estimated 100–150 million women currently use them worldwide [153, 154]. The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial (n = 596) was foundational for demonstrating the deleterious effects of unopposed estrogen use on the risk of developing UCC, finding that women assigned to estrogen-only OCPs were more likely than those given placebo to develop simple, complex, or atypical hyperplasia compared to those given a combination of estrogen OCPs and depot progesterone injections [155]. As a result, estrogen-only OCPs are no longer considered the standard of care, and either progestogens only or combined estrogen–progestogen formulations (combined OCPs) are used instead.

Multiple large, high-quality studies from diverse geographical regions have demonstrated that combined OCPs confer long-term protection against UCC [102, 106, 154, 156–160]. One CCS (n = 4077) reported a 30% reduction in UCC risk with ever-use of combined OCPs up to an 80% risk reduction following 10 years of use, and a large PCS (n = 46,022) found that combined OCP use reduced the standardized incidence rate of UCC from 29.56 to 19.42 per 100,000 [154]. A large PCS (n = 17,032) found that combined OCP use reduced UCC risk in a dose-dependent manner (RR per month of use: 0.6 for <48 months, 0.4 for 49–96 months, 0.1 for ≥97 months), with the protective effects seen in as few as 3 years of use and with maximal effects occurring after 6–10 years of use [106, 159, 160]. The protection

conferred by combined OCPs has been found to persist for 20–30 years or more following cessation of use, and multiple studies have found no effect modification from age at menarche, parity, BMI, use of menopausal HRT, menopausal status, race/ethnicity, smoking, or alcohol use [102, 106, 154, 156, 159, 160].

Combined OCPs confer a more modest degree of protection in those diagnosed with UCC at a relatively young age. One CCS (n = 775) found a decreased risk of UCC in patients aged <50 years after 1–5 years of combined OCP use compared to never-users, but concluded that >5 years of use did not further decrease this risk [161]. Several studies have considered the impact of various hormone potencies within OCP formulations on UCC risk reduction. An analysis of several CCSs (n = 2991) found that OCPs with high progestogen potency conferred an additional benefit compared to those with low potency for women with a BMI ≥22.1 kg/m^2, but a similar benefit was not seen in those with a lower BMI [157].

Larger studies have primarily investigated the use of estrogen-only and combined estrogen–progestogen OCPs, with data regarding progestogen-only OCPs or depot medroxyprogesterone either nonexistent or of too small a sample size to generate reliable conclusions [158]. As a result, very little is known about the impact of either oral or injectable progestogen-only contraception on UCC risk [158]. Studies regarding intrauterine devices (IUDs), both nonhormonal and hormone-containing, are sparse as well [158]. One recent meta-analysis reported a crude association between nonhormonal IUD use and decreased UCC risk; however, the included studies showed significant heterogeneity, the mechanism of UCC risk reduction from nonhormonal IUDs remains unclear, and further study is needed [162]. Even less data exists regarding levonorgestrel-releasing intrauterine devices (LNG-IUDs). One RCS (n = 2781) found that patients who had previously used an LNG-IUD had a standardized UCC incidence ratio (observed-to-expected ratio) of 0.50, and concluded that such devices may protect against malignant endometrial transformation; however, further investigation is needed [163].

1.8.4 Tubal Ligation

Bilateral tubal ligation (BTL) is a common method of birth control in the United States and is designed to obliterate communication between the uterine and peritoneal cavities [164, 165]. Since exfoliation through the Fallopian tubes represents a potential method of UCC metastasis, it has been questioned whether BTL impacts either the incidence of UCC or its stage at the diagnosis, especially in the case of Type II carcinomas, which spread in a manner similar to ovarian cancer [164, 165]. The largest RCT to explore this issue (n = 76,483) found no effect of BTL on the risk of developing either a Type I or a Type II carcinoma, suggesting that patients undergoing this procedure likely do not have any associated change in their baseline risk for developing UCC [165]. An analysis of the GOG-210 trial (n = 4489) did find an inverse relationship between BTL and both late-stage disease at presentation and peritoneal metastasis; however, BTL was not associated with any survival advantage after adjusting for stage at the diagnosis [164].

1.9 Other Associated Factors

1.9.1 Diet and Phytoestrogens

UCC risk shows considerable geographical variation; for example, Asian women living in Asia have one-tenth the risk of Caucasian women living in Western countries [166]. Such observations have led several authors to investigate the role that diet, exercise, and various other lifestyle factors play in endometrial carcinogenesis [166]. Consumption of whole grains, fresh fruit, and fresh vegetables has been shown to decrease the risk of UCC, and there is evidence that estrogen metabolism can be influenced by dietary fat intake, although this has never been directly investigated in conjunction with the risk of developing UCC [166]. The impact of a vegetarian or high-fiber diet is more inconsistently reported, with a vegetarian diet associated with lower urinary excretion of estradiol and a high fiber diet associated with lower serum E_2 levels in some studies, but not others [166]. A meta-analysis of retrospective data concluded that consumption of meat (particularly red meat) does increase UCC risk, but it found no association with dairy products, and inconsistent evidence for an association with poultry, fish, and eggs [167].

Other authors have considered the impact of diet on UCC risk from the perspective of glycemic index and total carbohydrate content. Dietary glycemic index (GI) is a measure that classifies carbohydrate quality by its effect on 2-hour postprandial blood glucose, whereas glycemic load (GL) is a concept that accounts for both the GI of a given food as well as its total carbohydrate content; in this way, GL represents a measure of both carbohydrate quality (GI) and total quantity [168]. Although long-term consumption of either a high-GL or a high-GI diet may lead to a state of chronic hyperinsulinemia, which has been implicated in the development of UCC, a recent meta-analysis concluded that a high-GL diet was associated with an increased risk of UCC (RR 1.20), particularly among obese women (RR 1.54), whereas a high-GI diet was not [168].

Phytoestrogens (PEs) are nonsteroidal compounds found in a variety of dietary compounds which are structurally similar to endogenous estrogens, but which show both estrogenic and antiestrogenic properties [169]. Although the precise mechanism of these effects is unknown, PEs have been hypothesized to exert antiestrogenic effects in high-estrogen environments and weakly estrogenic effects in low-estrogen environments [166, 170]. PEs are found in isoflavones (e.g., primarily soy products), coumestans (e.g., alfalfa sprouts, beans), lignans (e.g., flaxseed oil, unrefined grain products), flavonoids (e.g., quercetin, kaempferol), stilbenes (e.g., resveratrol), and mycotoxins (e.g., zearalanol) [170]. Two factors have spurred investigations into the role that PEs may play in endometrial carcinogenesis. First, geographical differences in UCC risk and interest in the so-called Asian diet as an explanation for these disparities have prompted investigations into the effects of tofu and other soy products on estrogen metabolism [166]. Second, the potential effect of PEs at the level of the estrogen receptor as well as their impact on estrogen metabolism have generated interest in their use as "natural" alternatives to estrogen-based HRT in postmenopausal women [170, 171]. This use, however, has generated concern that PEs may confer an increased risk of UCC similar to that seen in the use of unopposed estrogen HRT [169–171].

Thus far, investigations into the impact of PEs on UCC risk have yielded inconsistent and contradictory results, with retrospective studies tending to show a decreased risk of UCC with PE use, but prospective studies showing either no association or suggesting a possible increased risk. One CCS (n = 843) found that a higher consumption of tofu and other legumes decreased the risk of UCC by about half for the highest quartile of consumption compared to the lowest, and found similar risk reductions with increased consumption of other sources of PEs such as whole grains, fruits, vegetables, and seaweeds [172]. These effects were, however, limited to nulliparous women and to those without a history of using unopposed estrogen [172]. Another CCS (n = 970) similarly found that consumption of isoflavones and lignans was inversely associated with UCC risk [173]. Among prospective studies, one PCS (n = 46,027) found that total isoflavone intake was associated with a reduced risk of UCC in postmenopausal women; however, no significant association was found with increased consumption of legumes, soy, or tofu [174]. By contrast, an RCT (n = 376) found that long-term treatment (up to 5 years) with PEs in postmenopausal women was associated with an increased occurrence of endometrial hyperplasia, and although no cases of malignancy were detected, suggestion of a plausible mechanism for endometrial carcinogenesis as a result of PE use was concerning [169]. Several factors may explain these contradictory findings: residual confounding may be present due to the large variation in soy and isoflavone intake across racial/ethnic groups; increased PE consumption may be confounded by an overall increased health consciousness in these consumers; and reduction of UCC risk due to some PE-containing products may be mediated by a non-estrogenic mechanism, for example, via an antioxidant or anti-angiogenic mechanism [170, 174].

1.9.2 Ultraviolet Radiation, Calcium, and Vitamin D

Ecological studies have shown an inverse association between ultraviolet (UV) radiation and UCC risk, which has in turn led some authors to explore possible correlations with vitamin D and calcium as well [175]. Consumption of both vitamin D and calcium are highly correlated in the diet, both are metabolically interrelated, both have antiproliferative and pro-differentiation effects *in vitro*, and thus both may work synergistically to reduce cancer risk [176]. A pooled analysis of three CCSs (n = 2134) found no association between dietary vitamin D intake and UCC risk, and a possible inverse association with dietary calcium intake [176]. Ecological studies have important limitations which mitigate their ability to draw causal inferences (e.g., UV exposure may be a proxy for physical activity), and prospective studies are needed to further characterize the relationship between UCC risk and UV radiation, vitamin D intake, and calcium intake [176].

1.9.3 Exercise

Because UCC predominates in affluent, more industrialized nations with higher levels of obesity and more sedentary lifestyles, several authors have investigated

potential associations between exercise, inactivity, a sedentary lifestyle, and UCC risk. A meta-analysis of prospective data found that physical activity was associated with a 30% reduction in UCC risk, while greater sitting time was associated with an increased risk [177]. Another meta-analysis of both prospective and retrospective data similarly found that all intensities of exercise conferred a significant reduction in UCC risk; however, this effect was only seen in obese women [178]. Furthermore, a large PCS ($n = 24,460$) found that inactivity and high energy intake are risk factors for UCC, independent of BMI [179]. Risk declined with recreational activity corresponding to a minimum of four hours per week as well as with increased occupational activity, and women ≥50 years were seen to benefit the most from having an active lifestyle [179].

1.9.4 Diabetes and Hypertension

Diabetes mellitus (DM) strongly correlates with an increased risk of UCC, and although its impact is complicated by obesity, a common comorbidity of Type 2 DM, excess body weight alone cannot fully explain this association [180, 181]. Rather, it is likely that other metabolic characteristics of DM such as hyperinsulinemia and insulin resistance contribute to endometrial carcinogenesis independent of BMI [182, 183]. Insulin receptors have been discovered on each type of endometrial cancer cell *in vitro*, including ER-negative cell lines, and insulin has been subsequently postulated to increase endometrial proliferation by acting as a mitogen and augmenting the effects of insulin-like growth factors [166, 184]. Two large studies, one a meta-analysis ($n = 96,003$) and the other a PCS ($n = 36,761$), each concluded that diabetics were at a two- to threefold increased risk of developing UCC compared to nondiabetics [180, 181]. Although many studies have focused on an association between UCC risk and Type 2 DM, three studies have examined Type I DM and have found a significant positive association in these cases as well [180].

The impact of DM seems to be magnified by several of its common comorbidities. One PCS ($n = 36,773$) demonstrated a sixfold increased risk of UCC among diabetics with concurrent obesity, and a ninefold increased risk in those with both obesity and a low level of physical activity [185]. Furthermore, uncontrolled diabetics have a significantly higher risk of developing UCC than those who are well-controlled [186]. One CCS ($n = 2663$) that examined common comorbidities of insulin resistance that collectively comprise the metabolic syndrome concluded that overweight/obesity, hypertension, DM, and glucose metabolic disturbance were all associated with an increased risk of UCC [186]. Hypertension in particular was associated with a sixfold increased risk, and this risk was nearly doubled when coupled with overweight/obesity [186]. A number of smaller CCSs have similarly established an association between hypertension and UCC, even after controlling for elevated BMI [187]. DM has been shown to impact survival in UCC patients, with one RCS ($n = 1411$) reporting a worse disease-free survival (DFS) and OS in diabetics with Type I carcinomas, but finding no impact on survival in those with either Type II carcinomas or high-grade lesions [12].

1.9.5 Cigarette Smoking

Cigarette smoking is thought to exert an antiestrogenic effect by either producing weight loss, inducing menopause at an earlier age, or via alterations in hormone metabolism [188]. A recent meta-analysis of both prospective and retrospective data found that ever-smoking was associated with a reduced risk of UCC, while a PCS (n = 62,573) concluded that this risk reduction was independent of either BMI or age at menopause [188, 189]. In particular, smoking 20 cigarettes per day was associated with a 16% risk reduction in prospective studies and a 27% risk reduction in case–control studies [188]. This risk reduction was significant in postmenopausal, but not premenopausal women, and was stronger among HRT users than in nonusers [188].

1.9.6 Alcohol

There is inconsistent evidence for an association between alcohol intake and UCC risk. A recent meta-analysis of both prospective and retrospective data found no significant association overall; however, stratified analyses revealed a slightly increased risk with liquor consumption, which was not replicated for beer or wine [190]. One PCS (n = 46,933) found that postmenopausal women who consumed ≥2 drinks per day had a twofold increased risk of UCC compared to both nondrinkers and women who drank <2 drinks per day, with both of the latter groups having essentially no increased risk [85]. However, another PCS (n = 62,573) found no association between alcohol consumption and UCC risk, including no dose-dependent trends or associations with types of beverages [189].

1.9.7 Coffee and Tea

Coffee and tea are the most widely consumed beverages in the world, both containing many antioxidant compounds, and the intake of caffeine-containing beverages has been previously associated with increased levels of SHBG and decreased levels of bioavailable testosterone [191, 192]. These considerations have led several investigators to explore a potential association between caffeine-containing drinks and UCC risk. Meta-analyses of retrospective data have shown some protective effects; however, prospective studies have found weak, if any, associations between caffeine intake and UCC risk [193, 194]. Two large PCSs have been conducted regarding coffee and tea consumption. The first (n = 67,470) found that drinking <4 cups of coffee per day was not associated with a reduced UCC risk; however, consumption of ≥4 cups per day was associated with a 25% risk reduction compared to those who consumed <1 cup per day [195]. Tea consumption was not associated with UCC risk; however, this study was conducted in the United States, where black tea is consumed much more heavily than green tea [195]. The second PCS (n = 560,356) found no significant association between UCC risk and consumption of either coffee or tea [194].

1.9.8 Aspirin

Chronic inflammation resulting from obesity may work either in conjunction with, or in addition to, hormonal imbalances to produce UCC, and some authors have suggested that exposure of the endometrium to chronic inflammation is in fact one of the primary pathogenic implications of a hyperestrogenic state [79]. Chronic inflammation mediates carcinogenesis by stimulating the release of proinflammatory cytokines, enhancing angiogenesis, suppressing the immune system, and generating reactive oxygen species, which damage DNA [196]. An inflammatory state may also directly increase estrogen production and induce rapid cell division, thus increasing the probability of replication errors, ineffective DNA repair, and resulting mutations [79].

This hypothesis as well as previous studies showing a reduced risk of several cancers with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) has led to the identification of aspirin and other NSAIDs as potential therapeutic agents for the prevention of either primary or recurrent UCC [196]. One CCS (n = 2138) found that ever-use of aspirin in the previous 5 years was associated with a significantly lower UCC risk (OR 0.78) compared to controls, while the use of ≥2 aspirin per week reduced this risk by almost half (OR 0.54) [197]. Upon meta-analysis, risk reduction from aspirin use was only seen in obese women, and no risk reduction was seen with use of either acetaminophen or any other NSAID [197]. Other studies have demonstrated a potential role for low-dose aspirin in the prevention of recurrent UCC following primary therapy and staging [196]. One RCS (n = 1687) found that low-dose aspirin was associated with improved OS and DSS in UCC patients following primary therapy, with the greatest effects seen in those <60 years, those with a BMI >30 kg/m^2, those with Type I carcinoma, and in those who had received whole pelvic radiotherapy [196]. Additional high-quality, prospective studies are needed, however, before aspirin can be safely recommended as a therapeutic agent in the treatment of UCC.

1.10 Summary

UCC remains a significant source of morbidity and mortality worldwide, and its impact is especially pronounced in Western and more industrialized nations. It also represents a locus of significant health disparities, especially among blacks in the United States, who are more likely than whites to present with aggressive histologic subtypes and late-stage disease, and who experience increased overall mortality and worse disease-related outcomes. Epidemiologic research is increasingly shifting its focus towards the Hispanic population, as this cohort now represents the largest minority racial/ethnic group in the United States. Recent studies reveal that Hispanics are diagnosed at a younger age than whites, and are more likely to present with late-stage disease; however, they do not appear to experience a worse prognosis as a result of these tendencies. Advances in technology have allowed for more precise characterization of UCC subtypes on the genomic level, increasing

knowledge of pathologic mechanisms of tumorigenesis, improving the current understanding of health disparities among racial/ethnic groups, and suggesting potential avenues for the development of novel therapeutic agents.

The increased incidence of UCC in Western and more industrialized nations has led to several avenues of investigation, which may be broadly summarized as those exploring dietary and environmental differences between cultures and those considering differences in common medical comorbidities. With rare exception, traditional advice regarding a healthy diet and lifestyle (e.g., eating a diet high in fruits and vegetables, remaining active and exercising regularly, and maintaining a healthy BMI) appears to be efficacious in reducing UCC risk; however, protective environmental factors remain elusive. The use of estrogen without an accompanying progestogen, either for contraception or hormone replacement, has been shown to greatly increase UCC risk, whereas combined OCPs confer protection that lasts decades following cessation of use. As both hormonal and nonhormonal implantable contraceptive devices become increasingly common within the United States, high-quality studies are needed to confirm their hypothesized protective effects against UCC.

Clinicians should remain vigilant in counseling those at increased risk for UCC, including tamoxifen users, patients with PCOS, and those with hereditary cancer syndromes such as HNPCC, especially since more than half of those affected by this syndrome present with a gynecologic malignancy first. Further investigation is needed into the impact of breast–ovarian cancer syndromes on UCC risk; however, there is currently no clear evidence of an increased risk of UCC in those with a *BRCA* mutation. The proposal of an inflammatory mechanism in UCC tumorigenesis is intriguing, and may portend a future role for aspirin in either the primary or secondary prevention of UCC; however, further studies are needed to confirm the efficacy of aspirin for this use, and to weigh potential adverse effects against possible benefits.

Key Points

- Uterine corpus cancer (UCC) is the 6th most common cancer worldwide and the 14th most deadly, responsible for an estimated 319,600 new cases and 76,200 deaths per year.
- The average age of UCC diagnosis is 62 years, with 61% of cases occurring in women aged 55–74 years.
- Type I carcinomas account for 80–90% of UCC cases and arise in the setting of chronic estrogen exposure, whereas Type II carcinomas are rarer, have a higher median age of occurrence, and are less influenced by estrogen.
- Blacks are more likely than whites to develop Type II carcinomas, and they experience worse outcomes than other racial/ethnic cohorts in the United States at every stage of disease for unclear reasons.
- Hispanics present with UCC at a younger age than non-Hispanic whites and are more likely to present with late-stage disease, but they do not appear to experience worse outcomes as a result.
- Polycystic ovary syndrome significantly increases the risk of developing UCC, especially in younger patients.

- The use of estrogen unopposed by a progestogen greatly increases UCC risk, as does tamoxifen use; neither raloxifene nor commonly used aromatase inhibitors appear to increase this risk.
- Patients with the hereditary nonpolyposis colorectal cancer syndrome (Lynch syndrome) may have a higher lifetime risk of developing UCC than colorectal cancer, and often present with UCC first.
- Parity, breastfeeding, and the use of combined oral contraceptives (OCPs) all confer protection against UCC; however, the impact of intrauterine devices and progestogen-only OCPs remains unknown.
- Type 2 diabetes mellitus increases UCC risk two- to threefold, and its effects are magnified by obesity, hypertension, physical inactivity, and poor disease control.

Author Contributions
All of the authors have diligently contributed to the conception, development, and preparation of this manuscript, including the literature search, concept organization, and data interpretation. All of the authors have read and approved the final draft for publication.

Conflict of Interest The authors declare that they have no conflicts of interest associated with this manuscript.

Financial Disclosures None to disclose.

References

1. Torre LA, Islami F, Siegel RL, Ward EM, Jemal A. Global cancer in women: burden and trends. Cancer Epidemiol Biomarkers Prev. 2017;26(4):444–57.
2. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin. 2015;65(2):87–108.
3. Henley SJ, Miller JW, Dowling NF, Benard VB, Richardson LC. Uterine cancer incidence and mortality – United States, 1999-2016. MMWR Morb Mortal Wkly Rep. 2018;67(48):1333–8.
4. American Cancer Society. Cancer Facts & Figures 2018. Atlanta: American Cancer Society; 2018.
5. Cancer Stat Facts: Uterine cancer. SEER [Internet]. 2019. https://seer.cancer.gov/statfacts/html/corp.html. Accessed 10 Apr 2019
6. 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.
7. Lauchlan SC. Tubal (serous) carcinoma of the endometrium. Arch Pathol Lab Med. 1981;105(11):615–8.
8. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10–7.
9. Boruta DM II, Gehrig PA, Fader AN, Olawaiye AB. Management of women with uterine papillary serous cancer: a Society of Gynecologic Oncology (SGO) review. Gynecol Oncol. 2009;115(1):142–53.

10. Felix AS, Weissfeld JL, Stone RA, Bowser R, Chivukula M, Edwards RP, et al. Factors associated with Type I and Type II endometrial cancer. Cancer Causes Control. 2010;21(11):1851–6.
11. McCullough ML, Patel AV, Patel R, Rodriguez C, Feigelson HS, Bandera EV, et al. Body mass and endometrial cancer risk by hormone replacement therapy and cancer subtype. Cancer Epidemiol Biomarkers Prev. 2008;17(1):73–9.
12. Ko EM, Walter P, Clark L, Jackson A, Franasiak J, Bolac C, et al. The complex triad of obesity, diabetes and race in Type I and II endometrial cancers: prevalence and prognostic significance. Gynecol Oncol. 2014;133(1):28–32.
13. Lachance JA, Everett EN, Greer B, Mandel L, Swisher E, Tamimi H, et al. The effect of age on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. Gynecol Oncol. 2006;101(3):470–5.
14. Bjorge T, Engeland A, Tretli S, Weiderpass E. Body size in relation to cancer of the uterine corpus in 1 million Norwegian women. Int J Cancer. 2007;120(2):378–83.
15. Cao QJ, Belbin T, Socci N, Balan R, Prystowsky MB, Childs G, et al. Distinctive gene expression profiles by cDNA microarrays in endometrioid and serous carcinomas of the endometrium. Int J Gynecol Pathol. 2004;23(4):321–9.
16. O'Hara AJ, Bell DW. The genomics and genetics of endometrial cancer. Adv Genomics Genet. 2012;2012(2):33–47.
17. Odicino FE, Bignotti E, Rossi E, Pasinetti B, Tassi RA, Donzelli C, et al. HER-2/neu overexpression and amplification in uterine serous papillary carcinoma: comparative analysis of immunohistochemistry, real-time reverse transcription-polymerase chain reaction, and fluorescence in situ hybridization. Int J Gynecol Cancer. 2008;18(1):14–21.
18. Santin AD, Bellone S, Van Stedum S, Bushen W, Palmieri M, Siegel ER, et al. Amplification of c-erbB2 oncogene: a major prognostic indicator in uterine serous papillary carcinoma. Cancer. 2005;104(7):1391–7.
19. Singh P, Smith CL, Cheetham G, Dodd TJ, Davy ML. Serous carcinoma of the uterus-determination of HER-2/neu status using immunohistochemistry, chromogenic in situ hybridization, and quantitative polymerase chain reaction techniques: its significance and clinical correlation. Int J Gynecol Cancer. 2008;18(6):1344–51.
20. Slomovitz BM, Broaddus RR, Burke TW, Sneige N, Soliman PT, Wu W, et al. Her-2/neu overexpression and amplification in uterine papillary serous carcinoma. J Clin Oncol. 2004;22(15):3126–32.
21. 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(5):1897–902.
22. Maxwell GL, Tian C, Risinger J, Brown CL, Rose GS, Thigpen JT, et al. Racial disparity in survival among patients with advanced/recurrent endometrial adenocarcinoma: a Gynecologic Oncology Group study. Cancer. 2006;107(9):2197–205.
23. 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.
24. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. Int J Gynaecol Obstet. 2006;95(Suppl 1):S105–43.
25. Slomovitz BM, Burke TW, Eifel PJ, Ramondetta LM, Silva EG, Jhingran A, et al. Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. Gynecol Oncol. 2003;91(3):463–9.
26. Thomas M, Mariani A, Wright JD, Madarek EO, Powell MA, Mutch DG, 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.
27. Creasman WT, Kohler MF, Odicino F, Maisonneuve P, Boyle P. Prognosis of papillary serous, clear cell, and grade 3 stage I carcinoma of the endometrium. Gynecol Oncol. 2004;95(3):593–6.
28. Dunton CJ, Balsara G, McFarland M, Hernandez E. Uterine papillary serous carcinoma: a review. Obstet Gynecol Surv. 1991;46(2):97–102.

29. Hamilton CA, Cheung MK, Osann K, Chen L, Teng NN, Longacre TA, 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.
30. Gehrig PA, Bae-Jump VL, Boggess JF, Groben PA, Fowler WC Jr, Van Le L. Association between uterine serous carcinoma and breast cancer. Gynecol Oncol. 2004;94(1):208–11.
31. Levine DA, Lin O, Barakat RR, Robson ME, McDermott D, Cohen L, et al. Risk of endometrial carcinoma associated with BRCA mutation. Gynecol Oncol. 2001;80(3):395–8.
32. Chan JK, Manuel MR, Cheung MK, Osann K, Husain A, Teng NN, et al. Breast cancer followed by corpus cancer: is there a higher risk for aggressive histologic subtypes? Gynecol Oncol. 2006;102(3):508–12.
33. Goshen R, Chu W, Elit L, Pal T, Hakimi J, Ackerman I, et al. Is uterine papillary serous adenocarcinoma a manifestation of the hereditary breast-ovarian cancer syndrome? Gynecol Oncol. 2000;79(3):477–81.
34. Gallup DG, Stock RJ. Adenocarcinoma of the endometrium in women 40 years of age or younger. Obstet Gynecol. 1984;64(3):417–20.
35. 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.
36. Soliman PT, Oh JC, Schmeler KM, Sun CC, Slomovitz BM, Gershenson DM, et al. Risk factors for young premenopausal women with endometrial cancer. Obstet Gynecol. 2005;105(3):575–80.
37. La Vecchia C, Franceschi S, Gallus G, Decarli A, Colombo E, Liberati A, et al. Prognostic features of endometrial cancer in estrogen users and obese women. Am J Obstet Gynecol. 1982;144(4):387–90.
38. Yap OW, Matthews RP. Racial and ethnic disparities in cancers of the uterine corpus. J Natl Med Assoc. 2006;98(12):1930–3.
39. Allard JE, Maxwell GL. Race disparities between black and white women in the incidence, treatment, and prognosis of endometrial cancer. Cancer Control. 2009;16(1):53–6.
40. Jamison PM, Noone AM, Ries LA, Lee NC, Edwards BK. Trends in endometrial cancer incidence by race and histology with a correction for the prevalence of hysterectomy, SEER 1992 to 2008. Cancer Epidemiol Biomarkers Prev. 2013;22(2):233–41.
41. Keshavarz H, Hillis SD, Kieke BA, Marchbanks PA. Hysterectomy [Internet]. 2002. https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5105a1.htm. Accessed 26 Feb 2016.
42. Elshaikh MA, Munkarah AR, Robbins JR, Laser BS, Bhatt N, Cogan C, et al. The impact of race on outcomes of patients with early stage uterine endometrioid carcinoma. Gynecol Oncol. 2013;128(2):171–4.
43. Smotkin D, Nevadunsky NS, Harris K, Einstein MH, Yu Y, Goldberg GL. Histopathologic differences account for racial disparity in uterine cancer survival. Gynecol Oncol. 2012;127(3):616–9.
44. Baskovic M, Lichtensztajn DY, Nguyen T, Karam A, English DP. Racial disparities in outcomes for high-grade uterine cancer: a California cancer registry study. Cancer Med. 2018;7(9):4485–95.
45. Ferguson SE, Olshen AB, Levine DA, Viale A, Barakat RR, Boyd J. Molecular profiling of endometrial cancers from African-American and Caucasian women. Gynecol Oncol. 2006;101(2):209–13.
46. Maxwell GL, Risinger JI, Hayes KA, Alvarez AA, Dodge RK, Barrett JC, 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.
47. Randall TC, Armstrong K. Differences in treatment and outcome between African-American and white women with endometrial cancer. J Clin Oncol. 2003;21(22):4200–6.
48. Hicks ML, Phillips JL, Parham G, Andrews N, Jones WB, Shingleton HM, et al. The National Cancer Data Base report on endometrial carcinoma in African-American women. Cancer. 1998;83(12):2629–37.
49. Fader AN, Habermann EB, Hanson KT, Lin JF, Grendys EC, Dowdy SC. Disparities in treatment and survival for women with endometrial cancer: a contemporary national cancer database registry analysis. Gynecol Oncol. 2016;143(1):98–104.

50. Miller KD, Goding Sauer A, Ortiz AP, Fedewa SA, Pinheiro PS, Tortolero-Luna G, et al. Cancer Statistics for Hispanics/Latinos, 2018. CA Cancer J Clin. 2018;68(6):425–45.
51. Malagon-Blackwell EM, Seagle BL, Nieves-Neira W, Shahabi S. The Hispanic Paradox in endometrial cancer: a National Cancer Database study. Gynecol Oncol. 2017;146(2): 351–8.
52. Rodriguez AM, Schmeler KM, Kuo YF. Disparities in endometrial cancer outcomes between non-Hispanic White and Hispanic women. Gynecol Oncol. 2014;135(3):525–33.
53. Bregar AJ, Alejandro Rauh-Hain J, Spencer R, Clemmer JT, Schorge JO, Rice LW, et al. Disparities in receipt of care for high-grade endometrial cancer: a National Cancer Data Base analysis. Gynecol Oncol. 2017;145(1):114–21.
54. Schlumbrecht M, BaekerBispo JA, Balise RR, Huang M, Slomovitz B, Kobetz E. Variation in type II endometrial cancer risk by Hispanic subpopulation: an exploratory analysis. Gynecol Oncol. 2017;147(2):329–33.
55. Pinheiro PS, Callahan KE, Siegel RL, Jin H, Morris CR, Trapido EJ, et al. Cancer mortality in hispanic ethnic groups. Cancer Epidemiol Biomarkers Prev. 2017;26(3):376–82.
56. Cook LS, Nelson HE, Cockburn M, Olson SH, Muller CY, Wiggins CL. Comorbidities and endometrial cancer survival in Hispanics and non-Hispanic whites. Cancer Causes Control. 2013;24(1):61–9.
57. Mahdi H, Hou H, Kowk LL, Moslemi-Kebria M, Michener C. Type II endometrial cancer in Hispanic women: tumor characteristics, treatment and survival compared to non-Hispanic white women. Gynecol Oncol. 2014;133(3):512–7.
58. Torre LA, Sauer AM, Chen MS Jr, Kagawa-Singer M, Jemal A, Siegel RL. Cancer statistics for Asian Americans, Native Hawaiians, and Pacific Islanders, 2016: converging incidence in males and females. CA Cancer J Clin. 2016;66(3):182–202.
59. Mahdi H, Schlick CJ, Kowk LL, Moslemi-Kebria M, Michener C. Endometrial cancer in Asian and American Indian/Alaskan Native women: tumor characteristics, treatment and outcome compared to non-Hispanic white women. Gynecol Oncol. 2014;132(2):443–9.
60. Kost ER, Hall KL, Hines JF, Farley JH, Nycum LR, Rose GS, et al. Asian-Pacific Islander race independently predicts poor outcome in patients with endometrial cancer. Gynecol Oncol. 2003;89(2):218–26.
61. Norris T, Vines P, Hoeffel E. The American Indian and Alaska Native Population: 2010. United States Census Bureau; 2012.
62. Henderson BE, Ross RK, Pike MC, Casagrande JT. Endogenous hormones as a major factor in human cancer. Cancer Res. 1982;42(8):3232–9.
63. Siiteri PK. Steroid hormones and endometrial cancer. Cancer Res. 1978;38(11 Pt 2):4360–6.
64. Herrinton LJ, Weiss NS. Postmenopausal unopposed estrogens. Characteristics of use in relation to the risk of endometrial carcinoma. Ann Epidemiol. 1993;3(3):308–18.
65. Weiss NS, Sayvetz TA. Incidence of endometrial cancer in relation to the use of oral contraceptives. N Engl J Med. 1980;302(10):551–4.
66. 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(2):205–12.
67. Furness S, Roberts H, Marjoribanks J, Lethaby A. Hormone therapy in postmenopausal women and risk of endometrial hyperplasia. Cochrane Database Syst Rev. 2012;(8):Cd000402.
68. 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(15):1110–6.
69. Lukanova A, Lundin E, Micheli A, Arslan A, Ferrari P, Rinaldi S, et al. Circulating levels of sex steroid hormones and risk of endometrial cancer in postmenopausal women. Int J Cancer. 2004;108(3):425–32.
70. Potischman N, Hoover RN, Brinton LA, Siiteri P, Dorgan JF, Swanson CA, et al. Case-control study of endogenous steroid hormones and endometrial cancer. J Natl Cancer Inst. 1996;88(16):1127–35.
71. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2014;20(5):748–58.

72. Ding DC, Chen W, Wang JH, Lin SZ. Association between polycystic ovarian syndrome and endometrial, ovarian, and breast cancer: a population-based cohort study in Taiwan. Medicine (Baltimore). 2018;97(39):e12608.
73. Yin W, Falconer H, Yin L, Xu L, Ye W. Association between polycystic ovary syndrome and cancer risk. JAMA Oncol. 2019;5(1):106–7.
74. Fader AN, Arriba LN, Frasure HE, von Gruenigen VE. Endometrial cancer and obesity: epidemiology, biomarkers, prevention and survivorship. Gynecol Oncol. 2009;114(1):121–7.
75. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625–38.
76. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer–viewpoint of the IARC Working Group. N Engl J Med. 2016;375(8):794–8.
77. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I. Endometrial cancer. Lancet. 2005;366(9484):491–505.
78. Zeleniuch-Jacquotte A, Akhmedkhanov A, Kato I, Koenig KL, Shore RE, Kim MY, et al. Postmenopausal endogenous oestrogens and risk of endometrial cancer: results of a prospective study. Br J Cancer. 2001;84(7):975–81.
79. Modugno F, Ness RB, Chen C, Weiss NS. Inflammation and endometrial cancer: a hypothesis. Cancer Epidemiol Biomarkers Prev. 2005;14(12):2840–7.
80. Folsom AR, Kaye SA, Potter JD, Prineas RJ. Association of incident carcinoma of the endometrium with body weight and fat distribution in older women: early findings of the Iowa Women's Health Study. Cancer Res. 1989;49(23):6828–31.
81. Gredmark T, Kvint S, Havel G, Mattsson LA. Adipose tissue distribution in postmenopausal women with adenomatous hyperplasia of the endometrium. Gynecol Oncol. 1999;72(2):138–42.
82. 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.
83. Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry, physical activity, and endometrial cancer risk: results from the Netherlands cohort study. Int J Gynecol Cancer. 2006;16(Suppl 2):492.
84. Park SL, Goodman MT, Zhang ZF, Kolonel LN, Henderson BE, Setiawan VW. Body size, adult BMI gain and endometrial cancer risk: the multiethnic cohort. Int J Cancer. 2010;126(2):490–9.
85. Setiawan VW, Pike MC, Kolonel LN, Nomura AM, Goodman MT, Henderson BE. Racial/ethnic differences in endometrial cancer risk: the multiethnic cohort study. Am J Epidemiol. 2007;165(3):262–70.
86. Everett E, Tamimi H, Greer B, Swisher E, Paley P, Mandel L, 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.
87. Sturgeon SR, Sherman ME, Kurman RJ, Berman ML, Mortel R, Twiggs LB, et al. Analysis of histopathological features of endometrioid uterine carcinomas and epidemiologic risk factors. Cancer Epidemiol Biomarkers Prev. 1998;7(3):231–5.
88. Weiss JM, Saltzman BS, Doherty JA, Voigt LF, Chen C, Beresford SA, et al. Risk factors for the incidence of endometrial cancer according to the aggressiveness of disease. Am J Epidemiol. 2006;164(1):56–62.
89. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 2014;311(8):806–14.
90. Sponholtz TR, Palmer JR, Rosenberg L, Hatch EE, Adams-Campbell LL, Wise LA. Body size, metabolic factors, and risk of endometrial cancer in black women. Am J Epidemiol. 2016;183(4):259–68.
91. Karageorgi S, Hankinson SE, Kraft P, De Vivo I. Reproductive factors and postmenopausal hormone use in relation to endometrial cancer risk in the Nurses' Health Study cohort 1976-2004. Int J Cancer. 2010;126(1):208–16.

92. McPherson CP, Sellers TA, Potter JD, Bostick RM, Folsom AR. Reproductive factors and risk of endometrial cancer. The Iowa Women's Health Study. Am J Epidemiol. 1996;143(12):1195–202.
93. Zanagnolo V, Pasinetti B, Sartori E. Clinical review of 63 cases of sex cord stromal tumors. Eur J Gynaecol Oncol. 2004;25(4):431–8.
94. Podfigurna-Stopa A, Czyzyk A, Katulski K, Moszynski R, Sajdak S, Genazzani AR, et al. Recurrent endometrial hyperplasia as a presentation of estrogen-secreting the coma – case report and mini review of the literature. Gynecol Endocrinol. 2016;32(3):184–7.
95. Schumer ST, Cannistra SA. Granulosa cell tumor of the ovary. J Clin Oncol. 2003;21(6):1180–9.
96. Evans AT III, Gaffey TA, Malkasian GD Jr, Annegers JF. Clinicopathologic review of 118 granulosa and 82 theca cell tumors. Obstet Gynecol. 1980;55(2):231–8.
97. Schiff I, Sela HK, Cramer D, Tulchinsky D, Ryan KJ. Endometrial hyperplasia in women on cyclic or continuous estrogen regimens. Fertil Steril. 1982;37(1):79–82.
98. Henderson BE. The cancer question: an overview of recent epidemiologic and retrospective data. Am J Obstet Gynecol. 1989;161(6 Pt 2):1859–64.
99. Persson I, Adami HO, Bergkvist L, Lindgren A, Pettersson B, Hoover R, et al. Risk of endometrial cancer after treatment with oestrogens alone or in conjunction with progestogens: results of a prospective study. BMJ. 1989;298(6667):147–51.
100. Chu J, Schweid AI, Weiss NS. Survival among women with endometrial cancer: a comparison of estrogen users and nonusers. Am J Obstet Gynecol. 1982;143(5):569–73.
101. Shapiro S, Kelly JP, Rosenberg L, Kaufman DW, Helmrich SP, Rosenshein NB, et al. Risk of localized and widespread endometrial cancer in relation to recent and discontinued use of conjugated estrogens. N Engl J Med. 1985;313(16):969–72.
102. Weiderpass E, Adami HO, Baron JA, Magnusson C, Lindgren A, Persson I. Use of oral contraceptives and endometrial cancer risk (Sweden). Cancer Causes Control. 1999;10(4):277–84.
103. 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(13):1739–48.
104. Beral V, Bull D, Reeves G. Endometrial cancer and hormone-replacement therapy in the Million Women Study. Lancet. 2005;365(9470):1543–51.
105. Smith DC, Prentice R, Thompson DJ, Herrmann WL. Association of exogenous estrogen and endometrial carcinoma. N Engl J Med. 1975;293(23):1164–7.
106. Stanford JL, Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, et al. Oral contraceptives and endometrial cancer: do other risk factors modify the association? Int J Cancer. 1993;54(2):243–8.
107. Voigt LF, Weiss NS, Chu J, Daling JR, McKnight B, van Belle G. Progestagen supplementation of exogenous oestrogens and risk of endometrial cancer. Lancet. 1991;338(8762):274–7.
108. Jaakkola S, Lyytinen H, Pukkala E, Ylikorkala O. Endometrial cancer in postmenopausal women using estradiol-progestin therapy. Obstet Gynecol. 2009;114(6):1197–204.
109. Riggs BL, Hartmann LC. Selective estrogen-receptor modulators – mechanisms of action and application to clinical practice. N Engl J Med. 2003;348(7):618–29.
110. Cohen I. Endometrial pathologies associated with postmenopausal tamoxifen treatment. Gynecol Oncol. 2004;94(2):256–66.
111. Iqbal J, Ginsburg OM, Wijeratne TD, Howell A, Evans G, Sestak I, et al. Endometrial cancer and venous thromboembolism in women under age 50 who take tamoxifen for prevention of breast cancer: a systematic review. Cancer Treat Rev. 2012;38(4):318–28.
112. Fornander T, Hellstrom AC, Moberger B. Descriptive clinicopathologic study of 17 patients with endometrial cancer during or after adjuvant tamoxifen in early breast cancer. J Natl Cancer Inst. 1993;85(22):1850–5.
113. Fisher B, Costantino JP, Wickerham DL, Cecchini RS, Cronin WM, Robidoux A, 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.

114. Cummings SR, Eckert S, Krueger KA, Grady D, Powles TJ, Cauley JA, et al. The effect of raloxifene on risk of breast cancer in postmenopausal women: results from the MORE randomized trial. Multiple Outcomes of Raloxifene Evaluation. JAMA. 1999;281(23): 2189–97.
115. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. Lancet. 2015;386(10001):1341–52.
116. 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.
117. Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE. 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.
118. Barakat RR, Wong G, Curtin JP, Vlamis V, Hoskins WJ. 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.
119. Chin J, Konje JC, Hickey M. Levonorgestrel intrauterine system for endometrial protection in women with breast cancer on adjuvant tamoxifen. Cochrane Database Syst Rev. 2009;(4):Cd007245.
120. ACOG Committee Opinion No. 601. Tamoxifen and uterine cancer. Obstet Gynecol. 2014;123(6):1394–7.
121. DeMichele A, Troxel AB, Berlin JA, Weber AL, Bunin GR, Turzo E, et al. Impact of raloxifene or tamoxifen use on endometrial cancer risk: a population-based case-control study. J Clin Oncol. 2008;26(25):4151–9.
122. ACOG Committee Opinion No. 738. Aromatase inhibitors in gynecologic practice. Obstet Gynecol. 2018;131(6):e194–9.
123. Chlebowski RT, Schottinger JE, Shi J, Chung J, Haque R. Aromatase inhibitors, tamoxifen, and endometrial cancer in breast cancer survivors. Cancer. 2015;121(13):2147–55.
124. Amir E, Seruga B, Niraula S, Carlsson L, Ocana A. Toxicity of adjuvant endocrine therapy in postmenopausal breast cancer patients: a systematic review and meta-analysis. J Natl Cancer Inst. 2011;103(17):1299–309.
125. Ollikainen M, Abdel-Rahman WM, Moisio AL, Lindroos A, Kariola R, Jarvela I, et al. Molecular analysis of familial endometrial carcinoma: a manifestation of hereditary nonpolyposis colorectal cancer or a separate syndrome? J Clin Oncol. 2005;23(21):4609–16.
126. Win AK, Reece JC, Ryan S. Family history and risk of endometrial cancer: a systematic review and meta-analysis. Obstet Gynecol. 2015;125(1):89–98.
127. Sandles LG, Shulman LP, Elias S, Photopulos GJ, Smiley LM, Posten WM, et al. Endometrial adenocarcinoma: genetic analysis suggesting heritable site-specific uterine cancer. Gynecol Oncol. 1992;47(2):167–71.
128. Berends MJ, Wu Y, Sijmons RH, van der Sluis T, Ek WB, Ligtenberg MJ, et al. Toward new strategies to select young endometrial cancer patients for mismatch repair gene mutation analysis. J Clin Oncol. 2003;21(23):4364–70.
129. Meyer LA, Broaddus RR, Lu KH. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer Control. 2009;16(1):14–22.
130. Lu KH, Dinh M, Kohlmann W, Watson P, Green J, Syngal S, et al. Gynecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet Gynecol. 2005;105(3):569–74.
131. Vasen HF, Stormorken A, Menko FH, Nagengast FM, Kleibeuker JH, Griffioen G, et al. MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. J Clin Oncol. 2001;19(20):4074–80.
132. Vasen HF, Watson P, Mecklin JP, Jass JR, Green JS, Nomizu T, et al. The epidemiology of endometrial cancer in hereditary nonpolyposis colorectal cancer. Anticancer Res. 1994;14(4b):1675–8.

133. 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.
134. Riegert-Johnson DL, Gleeson FC, Roberts M, Tholen K, Youngborg L, Bullock M, et al. Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients. Hered Cancer Clin Pract. 2010;8(1):6.
135. Pilarski R, Stephens JA, Noss R, Fisher JL, Prior TW. Predicting PTEN mutations: an evaluation of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. J Med Genet. 2011;48(8):505–12.
136. Heald B, Mester J, Rybicki L, Orloff MS, Burke CA, Eng C. Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. Gastroenterology. 2010;139(6):1927–33.
137. Hornreich G, Beller U, Lavie O, Renbaum P, Cohen Y, Levy-Lahad E. Is uterine serous papillary carcinoma a BRCA1-related disease? Case report and review of the literature. Gynecol Oncol. 1999;75(2):300–4.
138. Barak F, Milgrom R, Laitman Y, Gemer O, Rabinovich A, Piura B, et al. The rate of the predominant Jewish mutations in the BRCA1, BRCA2, MSH2 and MSH6 genes in unselected Jewish endometrial cancer patients. Gynecol Oncol. 2010;119(3):511–5.
139. Thompson D, Easton DF. Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst. 2002;94(18):1358–65.
140. Beiner ME, Finch A, Rosen B, Lubinski J, Moller P, Ghadirian P, et al. The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. Gynecol Oncol. 2007;104(1):7–10.
141. Shu CA, Pike MC, Jotwani AR, Friebel TM, Soslow RA, Levine DA, et al. Uterine cancer after risk-reducing salpingo-oophorectomy without hysterectomy in women with BRCA mutations. JAMA Oncol. 2016;2(11):1434–40.
142. Cetin I, Cozzi V, Antonazzo P. Infertility as a cancer risk factor – a review. Placenta. 2008;29(Suppl B):169–77.
143. Raglan O, Kalliala I, Markozannes G, et al. Risk factors for endometrial cancer: an umbrella review of the literature [published online ahead of print]. Int J Cancer. 2018. https://onlinelibrary.wiley.com/doi/abs/10.1002/ijc.31961. Accessed 29 Apr 2019.
144. Wu QJ, Li YY, Tu C, Zhu J, Qian KQ, Feng TB, et al. Parity and endometrial cancer risk: a meta-analysis of epidemiological studies. Sci Rep. 2015;5:14243.
145. Setiawan VW, Pike MC, Karageorgi S, Deming SL, Anderson K, Bernstein L, et al. Age at last birth in relation to risk of endometrial cancer: pooled analysis in the epidemiology of endometrial cancer consortium. Am J Epidemiol. 2012;176(4):269–78.
146. Brinton LA, Berman ML, Mortel R, Twiggs LB, Barrett RJ, Wilbanks GD, et al. Reproductive, menstrual, and medical risk factors for endometrial cancer: results from a case-control study. Am J Obstet Gynecol. 1992;167(5):1317–25.
147. Xu WH, Xiang YB, Ruan ZX, Zheng W, Cheng JR, Dai Q, et al. Menstrual and reproductive factors and endometrial cancer risk: results from a population-based case-control study in urban Shanghai. Int J Cancer. 2004;108(4):613–9.
148. Althuis MD, Moghissi KS, Westhoff CL, Scoccia B, Lamb EJ, Lubin JH, et al. Uterine cancer after use of clomiphene citrate to induce ovulation. Am J Epidemiol. 2005;161(7):607–15.
149. Lerner-Geva L, Rabinovici J, Lunenfeld B. Ovarian stimulation: is there a long-term risk for ovarian, breast and endometrial cancer? Womens Health (Lond). 2010;6(6):831–9.
150. Venn A, Watson L, Bruinsma F, Giles G, Healy D. Risk of cancer after use of fertility drugs with in-vitro fertilisation. Lancet. 1999;354(9190):1586–90.
151. Jordan SJ, Na R, Johnatty SE, Wise LA, Adami HO, Brinton LA, et al. Breastfeeding and endometrial cancer risk: an analysis from the epidemiology of endometrial cancer consortium. Obstet Gynecol. 2017;129(6):1059–67.
152. Zhan B, Liu X, Li F, Zhang D. Breastfeeding and the incidence of endometrial cancer: a meta-analysis. Oncotarget. 2015;6(35):38398–409.

153. Hannaford PC, Selvaraj S, Elliott AM, Angus V, Iversen L, Lee AJ. Cancer risk among users of oral contraceptives: cohort data from the Royal College of General Practitioner's oral contraception study. BMJ. 2007;335(7621):651.
154. Iversen L, Sivasubramaniam S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. Am J Obstet Gynecol. 2017;216(6):580.e1–9.
155. Effects of hormone replacement therapy on endometrial histology in postmenopausal women. The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. The Writing Group for the PEPI Trial. JAMA. 1996;275(5):370–5.
156. Endometrial cancer and oral contraceptives: an individual participant meta-analysis of 27 276 women with endometrial cancer from 36 epidemiological studies. Collaborative Group on Epidemiological Studies on Endometrial Cancer. Lancet Oncol. 2015;16(9): 1061–70.
157. Maxwell GL, Schildkraut JM, Calingaert B, Risinger JI, Dainty L, Marchbanks PA, et al. Progestin and estrogen potency of combination oral contraceptives and endometrial cancer risk. Gynecol Oncol. 2006;103(2):535–40.
158. Mueck AO, Seeger H, Rabe T. Hormonal contraception and risk of endometrial cancer: a systematic review. Endocr Relat Cancer. 2010;17(4):R263–71.
159. Tao MH, Xu WH, Zheng W, Zhang ZF, Gao YT, Ruan ZX, et al. Oral contraceptive and IUD use and endometrial cancer: a population-based case-control study in Shanghai, China. Int J Cancer. 2006;119(9):2142–7.
160. Vessey M, Painter R. Oral contraceptive use and cancer. Findings in a large cohort study, 1968-2004. Br J Cancer. 2006;95(3):385–9.
161. Parslov M, Lidegaard O, Klintorp S, Pedersen B, Jonsson L, Eriksen PS, et al. Risk factors among young women with endometrial cancer: a Danish case-control study. Am J Obstet Gynecol. 2000;182(1 Pt 1):23–9.
162. Beining RM, Dennis LK, Smith EM, Dokras A. Meta-analysis of intrauterine device use and risk of endometrial cancer. Ann Epidemiol. 2008;18(6):492–9.
163. Soini T, Hurskainen R, Grenman S, Maenpaa J, Paavonen J, Pukkala E. Cancer risk in women using the levonorgestrel-releasing intrauterine system in Finland. Obstet Gynecol. 2014;124(2 Pt 1):292–9.
164. Felix AS, Brinton LA, McMeekin DS, Creasman WT, Mutch D, Cohn DE, et al. Relationships of tubal ligation to endometrial carcinoma stage and mortality in the NRG Oncology/ Gynecologic Oncology Group 210 Trial. J Natl Cancer Inst. 2015;107(9).
165. Winer I, Lehman A, Wactawski-Wende J, Robinson R, Simon M, Cote M. Tubal ligation and risk of endometrial cancer: findings from the Women's Health Initiative. Int J Gynecol Cancer. 2016;26(3):464–71.
166. Hale GE, Hughes CL, Cline JM. Endometrial cancer: hormonal factors, the perimenopausal "window of risk," and isoflavones. J Clin Endocrinol Metab. 2002;87(1):3–15.
167. Bandera EV, Williams MG, Sima C, Bayuga S, Pulick K, Wilcox H, et al. Phytoestrogen consumption and endometrial cancer risk: a population-based case-control study in New Jersey. Cancer Causes Control. 2009;20(7):1117–27.
168. Mulholland HG, Murray LJ, Cardwell CR, Cantwell MM. Dietary glycaemic index, glycaemic load and endometrial and ovarian cancer risk: a systematic review and meta-analysis. Br J Cancer. 2008;99(3):434–41.
169. Unfer V, Casini ML, Costabile L, Mignosa M, Gerli S, Di Renzo GC. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. Fertil Steril. 2004;82(1):145–8, quiz 265
170. Bandera EV, Kushi LH, Moore DF, Gifkins DM, McCullough ML. Consumption of animal foods and endometrial cancer risk: a systematic literature review and meta-analysis. Cancer Causes Control. 2007;18(9):967–88.
171. The role of soy isoflavones in menopausal health: report of The North American Menopause Society/Wulf H. Utian Translational Science Symposium in Chicago, IL (October 2010). Menopause. 2011;18(7):732–53.

172. Goodman MT, Wilkens LR, Hankin JH, Lyu LC, Wu AH, Kolonel LN. Association of soy and fiber consumption with the risk of endometrial cancer. Am J Epidemiol. 1997;146(4): 294–306.
173. Horn-Ross PL, John EM, Canchola AJ, Stewart SL, Lee MM. Phytoestrogen intake and endometrial cancer risk. J Natl Cancer Inst. 2003;95(15):1158–64.
174. Ollberding NJ, Lim U, Wilkens LR, Setiawan VW, Shvetsov YB, Henderson BE, et al. Legume, soy, tofu, and isoflavone intake and endometrial cancer risk in postmenopausal women in the multiethnic cohort study. J Natl Cancer Inst. 2012;104(1):67–76.
175. Grant WB, Garland CF. The association of solar ultraviolet B (UVB) with reducing risk of cancer: multifactorial ecologic analysis of geographic variation in age-adjusted cancer mortality rates. Anticancer Res. 2006;26(4a):2687–99.
176. McCullough ML, Bandera EV, Moore DF, Kushi LH. Vitamin D and calcium intake in relation to risk of endometrial cancer: a systematic review of the literature. Prev Med. 2008;46(4):298–302.
177. Moore SC, Gierach GL, Schatzkin A, Matthews CE. Physical activity, sedentary behaviours, and the prevention of endometrial cancer. Br J Cancer. 2010;103(7):933–8.
178. Schmid D, Behrens G, Keimling M, Jochem C, Ricci C, Leitzmann M. A systematic review and meta-analysis of physical activity and endometrial cancer risk. Eur J Epidemiol. 2015;30(5):397–412.
179. Furberg AS, Thune I. Metabolic abnormalities (hypertension, hyperglycemia and overweight), lifestyle (high energy intake and physical inactivity) and endometrial cancer risk in a Norwegian cohort. Int J Cancer. 2003;104(6):669–76.
180. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia. 2007;50(7):1365–74.
181. Lindemann K, Vatten LJ, Ellstrom-Engh M, Eskild A. Body mass, diabetes and smoking, and endometrial cancer risk: a follow-up study. Br J Cancer. 2008;98(9):1582–5.
182. Shoff SM, Newcomb PA. Diabetes, body size, and risk of endometrial cancer. Am J Epidemiol. 1998;148(3):234–40.
183. Soliman PT, Wu D, Tortolero-Luna G, Schmeler KM, Slomovitz BM, Bray MS, et al. Association between adiponectin, insulin resistance, and endometrial cancer. Cancer. 2006;106(11):2376–81.
184. Nagamani M, Stuart CA. Specific binding and growth-promoting activity of insulin in endometrial cancer cells in culture. Am J Obstet Gynecol. 1998;179(1):6–12.
185. Friberg E, Mantzoros CS, Wolk A. Diabetes and risk of endometrial cancer: a population-based prospective cohort study. Cancer Epidemiol Biomarkers Prev. 2007;16(2):276–80.
186. Zhang Y, Liu Z, Yu X, Zhang X, Lu S, Chen X, et al. The association between metabolic abnormality and endometrial cancer: a large case-control study in China. Gynecol Oncol. 2010;117(1):41–6.
187. Soler M, Chatenoud L, Negri E, Parazzini F, Franceschi S, la Vecchia C. Hypertension and hormone-related neoplasms in women. Hypertension. 1999;34(2):320–5.
188. 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(6):501–8.e3.
189. Loerbroks A, Schouten LJ, Goldbohm RA, van den Brandt PA. Alcohol consumption, cigarette smoking, and endometrial cancer risk: results from the Netherlands Cohort Study. Cancer Causes Control. 2007;18(5):551–60.
190. Sun Q, Xu L, Zhou B, Wang Y, Jing Y, Wang B. Alcohol consumption and the risk of endometrial cancer: a meta-analysis. Asia Pac J Clin Nutr. 2011;20(1):125–33.
191. Bravi F, Scotti L, Bosetti C, Gallus S, Negri E, La Vecchia C, et al. Coffee drinking and endometrial cancer risk: a metaanalysis of observational studies. Am J Obstet Gynecol. 2009;200(2):130–5.
192. Yu X, Bao Z, Zou J, Dong J. Coffee consumption and risk of cancers: a meta-analysis of cohort studies. BMC Cancer. 2011;11:96.
193. Tang NP, Li H, Qiu YL, Zhou GM, Ma J. Tea consumption and risk of endometrial cancer: a metaanalysis. Am J Obstet Gynecol. 2009;201(6):605.e1–8.

194. Yang TO, Crowe F, Cairns BJ, Reeves GK, Beral V. Tea and coffee and risk of endometrial cancer: cohort study and meta-analysis. Am J Clin Nutr. 2015;101(3):570–8.
195. Je Y, Hankinson SE, Tworoger SS, De Vivo I, Giovannucci E. A prospective cohort study of coffee consumption and risk of endometrial cancer over a 26-year follow-up. Cancer Epidemiol Biomarkers Prev. 2011;20(12):2487–95.
196. Matsuo K, Cahoon SS, Yoshihara K, Shida M, Kakuda M, Adachi S, et al. Association of low-dose aspirin and survival of women with endometrial cancer. Obstet Gynecol. 2016;128(1):127–37.
197. Neill AS, Nagle CM, Protani MM, Obermair A, Spurdle AB, Webb PM. Aspirin, nonsteroidal anti-inflammatory drugs, paracetamol and risk of endometrial cancer: a case-control study, systematic review and meta-analysis. Int J Cancer. 2013;132(5):1146–55.

Cytogenetic Mechanisms in Endometrial Cancer

2

Ritu Khatuja and Abhishek Malakar

2.1 Introduction

Endometrial cancer (EC) is the second most common gynecological cancer and is fourth in incidence after breast, lung and colon cancer. The incidence of endometrial cancer has increased by 21% since 2008 and the mortality rate per 100,000 cases has increased by ≥100% over the last two decades and by 8% since 2008 [1]. This shows that the incidence of EC is increasing worldwide day by day. The prognosis of this malignancy is better and in majority of cases total abdominal hysterectomy with bilateral salpingo-oophorectomy is the treatment of choice in early malignancies. But in cases of women who are in advanced stage and/or require chemotherapy or radiotherapy, the side effects of these treatment modalities are very high. So it is required that we develop a targeted therapy to optimize treatment with minimal side effects. This can only be done by understanding cytogenetic and molecular basis of endometrial cancer. In this chapter we will be describing the cytogenetic mechanisms involved in the genesis of endometrial cancer.

2.2 Classification of EC

2.2.1 Clinicopathological Classification

Endometrial cancer can be divided into two types, type I and type II based on clinicopathological properties.

R. Khatuja (✉) · A. Malakar
Department of Obstetrics & Gynecology, ANIIMS & G B Pant Hospital, Port Blair, Andaman & Nicobar Islands, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_2

Type I endometrial cancer more commonly develops in premenopausal or perimenopausal women and occurs in an estrogen-dependent manner via atypical endometrial hyperplasia. They are mostly well-differentiated endometrioid adenocarcinoma, with relatively favorable prognosis. Almost 80% of endometrial cancers fall in this category.

Type II endometrial cancer develops in postmenopausal women in an estrogen-independent manner, and is thought to be due to de novo carcinogenesis that develops directly from the normal endometrium, rather than endometrial hyperplasia as its precursor. Histopathologically, they are extremely poorly differentiated endometrioid adenocarcinoma and serous adenocarcinoma, with poor prognosis. This will be discussed in detail in the chapter on hereditary endometrial cancer.

There are two more types of EC which do not fit in the above category.

These are the mixed carcinoma which retains some of the molecular alterations of type I tumors and represent at least 10% of the neoplasm and EC with ambiguous features which exhibit overlapping and intermediate features between type I and type II and fail to show two distinct components [2].

2.2.2 Genetic Classification

The Cancer Genome Atlas (TCGA) project has categorized endometrial carcinoma into four broad categories based on integrated genomic and proteomic analyses [3]:

(a) Microsatellite instability cancers: One-third of all cancers are in this group, which are predominantly type I endometrioid tumors with high mutation rates and frequent KRAS mutations.
(b) Microsatellite stable cancers, low copy-number alteration endometrioid cancers**:** These have a high frequency of β-catenin mutations.
(c) Microsatellite stable cancers, high copy-number alteration cancers**:** This group has frequent TP53 mutations with mostly serous and grade 3 endometrioid cancers.
(d) Ultrahigh mutation rate cancers: It is a small subgroup of tumors with very high mutation rate (almost 100-fold more than low mutation tumors) and are characterized by hotspot mutation in POLE, catalytic subunit of DNA polymerase epsilon involved in DNA replication and repair.

2.3 Role of Estrogen

Type I endometrial cancer is an estrogen-dependent tumor, but along with estrogen, different genetic as well as epigenetic changes or mutations are also involved in carcinogenesis. The mechanisms involved include as in the following sections.

2.3.1 Imbalance Between Estrogen-Induced Endometrial Proliferation and Mismatch Repair System

Mismatch Repair (MMR) deficiency is the most common genetic abnormality associated with endometrial carcinoma and there is an association between the level of estrogen and level of MMR activity in endometrial epithelial cells [4]. MMR activity increases where there is a high estrogen level. So it is very much unlikely to develop EC in young age group when the estrogen level is as well as MMR activity is high. On the other hand, in older postmenopausal women, risk of carcinoma increases due to estrogen deficiency and less endometrial growth. However, this group is prone for type II EC. The perimenopausal age group is the time period where there is an imbalance between the estrogen activity and MMR activity, and it was found that MMR activity is very low when estrogen level is between 20 and 60 pg/mL. This leads to sufficient estrogen for cell growth without sufficient MMR activity leading to carcinogenesis. This intermediate period is the *Cancer window* for endometrial carcinoma (Table 2.1).

2.3.2 Dysregulation of Different Genetic Factors by Estrogen

Estrogen passes through the cell membrane and binds to estrogen receptor (ER) in the cytoplasm and stimulates certain growth factors. These factors regulate normal proliferation and differentiation, but they can also act as oncogenes or become targets of overactivation and lead to uncontrolled proliferation. The mechanisms involved in the oncogenesis through estrogen are:

(a) ER regulates gene expression via estrogen response elements in promoter regions of target genes such as c-Fos promoter leading to induction of c-Fos mRNA.
(b) Estrogen enhances uterine expression of EGF and EGF receptor (a structural homolog of the c-Erb b oncogene product) as well as expression of IGF-I and IGF-II mRNA.
(c) Estrogen promotes cell proliferation and inhibits apoptosis through a complex downstream cascade of transcriptional changes that may include modulation of tumor suppressor function such as PTEN.

Table 2.1 Cancer window

High estrogen (E2 > 80 pg/mL) Young age group	Relatively low estrogen (E2 20–60 pg/mL) Perimenopausal age group	Low estrogen (E2 < 15 pg/mL) Postmenopausal age group
Cell proliferation < MMR activity	Cell proliferation > MMR activity *CANCER WINDOW*	Cell proliferation = MMR activity

(d) PAX2 expression is increased by estrogens in neoplastic endometrial epithelium but not in normal endometrium, indicating that neoplastic tissues have an intrinsically altered estrogen response mechanism [5].
(e) Endometrial cancer cell line expression of HOXB13, a member of the HOX gene family can be induced by estrogens and imparts invasive potential [6].
(f) Cables, a cyclin-dependent kinase binding protein that is upregulated by progesterone and downregulated by estrogen in benign endometrium, is lost in the majority of endometrial cancers. It is shown that mice deficient in cables develop hyperplasia and cancer, and overexpression in cell lines slows proliferation [7].

2.4 Mechanisms Involved in Genesis of EC at Cytogenetic Level

2.4.1 Epigenetics

Epigenetic changes refer to DNA methylation and histone acetylation [8]. These epigenetic changes in germ cells may inhibit transcription of genes for which expression is not usually inhibited or activate genes that are usually inhibited [9, 10]; this is called epimutation.

(A) DNA methylation—It refers to the addition of a methyl group to a cytosine base at a CpG sequence by DNA methyltransferase. DNA methylation in CpG islands, in promoters upstream of gene transcription start sites is critical in gene expression [11]. If the DNA in this region is methylated, a nucleosome forms and transcription is blocked [12, 13]. Following genes are affected due to DNA methylation leading to EC:
    1. Many tumor suppressor genes as well as Mismatch Repair (MMR) genes are inactivated by aberrant gene methylation. hMLH1 and hMSH2 are two important MMR genes, which are affected by epigenetic silencing which is more common in hMLH1 [14]. Muraki et al. found aberrant methylation of hMLH1 in 40.4% of patients with endometrial cancer [15].
    2. Other tumor suppressor genes affected by methylation are: SPRY2 (Sprouty2), Ras association domain family 1 isoform A (RASSF1A), ribosomal 56 kinase4 (RSK4), adenomatous polyposis coil (APC), checkpoint with FHA and RING (CHFR), p73, caspase-8 (CASP8), G-protein coupled receptor 54 (GPR54), cadherin 1 (CDH1), homeobox A11 (HOXA11), and catechol-O-methyltransferase (COMT) [15].
    3. Whitcomb et al. showed that methylation of the HOXA11 promoter, a gene involved in proliferation and differentiation of the endometrium, was more frequent in recurrent endometrial cancer [16].
(B) CpG island methylator phenotype (CIMP): Cancer with genome-wide methylation is classified as CIMP-positive. In endometrial cancer, Zhang et al. examined the methylation status of five genes (p14, p16, ER, COX-2, and

RASSF1A) and found CIMP-positive cancer tissues and adjacent normal endometrial tissues [17]. Wiesenberger et al. suggested that CIMP could be a new tumor marker for early carcinogenesis in endometrial cancer [18].

(C) Histone Acetylation:
- Four proteins of the histone family (H2A, H2B, H3, H4) have been identified as the central elements of the protein core of the nucleosome, which is the basis of DNA structural organization.
- Histone acetylation is important in regulation of the cell cycle. Histone acetylation leads to DNA "unpackaging" which is necessary for transcription and deacetylation leads to the formation of condensed chromatin and suppression of genetic expression. The equilibrium between histone acetylation and deacetylation is maintained by two antagonistic classes of enzymes, namely histone deacetylases (HDACs) and histone acetyltransferases (HATs) [19–21].
- Dysfunctional histone acetylation can promote carcinogenesis by either reducing the expression of tumor suppressor genes (hypoacetylation) or promoting the expression of oncogenes (hyperacetylation) [21].
- In EC, histone acetylation is directly involved in the silencing of hMLH1/MSH2, PTEN, and progesterone receptor (PR) gene. The expression of HDAC has been shown to be parallel to neoplastic development. Weichert et al. [22] showed that most ECs are characterized by elevated expression of class I HDAC isoforms in the nuclei of tumor cells.
- Clear cell and serous subtypes showed significantly higher expression rates of all three HDACs when compared with endometrioid carcinomas. Also, increased HDAC-1 protein expression was associated with poor prognosis in endometrioid carcinoma.

Clinical Implication: Histone deacetylase inhibitors (HDACI) are a promising therapeutic strategy, which act by inhibiting cellular proliferation as well as by promoting the expression of specific tumor suppressor genes. Different HDACIs are: Scriptaid/oxamflatin, Trichostatin, Voronostat (SAHA, MK0683), Entinostat (MS-275), Psammaplin, Apicidin/Depsipeptide, and Romidepsin (FK288) [23–26].

2.4.2 Abnormal Mismatch Repair (MMR) System

- MMR system is responsible for repairing any base mismatch which is very common during replication. If MMR system is deficient, no repair is possible leading to DNA strands with different lengths mostly in microsatellite portions of human genome which is termed as Microsatellite Instability (MSI). MMR deficiency also leads to the accumulation of mutations leading to carcinogenesis. Different MMR genes are genes encoding hMLH1, hMSH2, hPMS2, hMSH3, and hMSH6.
- Aberrations in MMR genes can be either following mutation or DNA methylation (epimutation, as already described). This aberration in MMR genes is found in type I endometrial cancer and atypical endometrial hyperplasia.

- MMR genes are also causative genes in Lynch syndrome (hereditary nonpolyposis colorectal cancer). hMLH1, hMSH2, and hMSH6 mutations are particularly important in families of patients with Lynch syndrome. Most mutations occur in hMLH1 and hMSH2 [27, 28]. Cumulative lifetime risk of endometrial carcinoma for different MMR gene defects as found by Hendriks et al. are hMLH1 (27%), hMSH2 (40%), and hMSH6 (71%) [20].
- MSI is present in 75% of hereditary endometrial cancers and 25–30% of sporadic endometrial cancers [29]. This part will be discussed in the chapter on hereditary endometrial cancers book.

2.4.3 Gene Mutation

- Gene mutations can affect in two ways, either by inactivation of some tumor suppressor genes, or activation of some oncogenes. It also involves changes in microRNA. For the two types of endometrial cancer, different subsets of gene mutations are responsible (Fig. 2.1).

2.4.3.1 Tumor Suppressor Genes

TP53 mutation: Normal p53 regulates cell proliferation, apoptosis induction, and DNA repair. Overexpression of mutant p53 is associated with poor prognostic features like advanced stage, high grade, and non-endometrioid histology. Point mutations in p53 are found in 90% of cases of type II endometrial cancer, but in only 10–20% of grade 3 type I endometrial cancer. It is found in 10% of stage I and II cancers and 40% of stage III and IV cancers [30]. Zheng et al. suggested that this "p53 signature" of endometrium reflected potential serous adenocarcinoma lesions [31, 32].

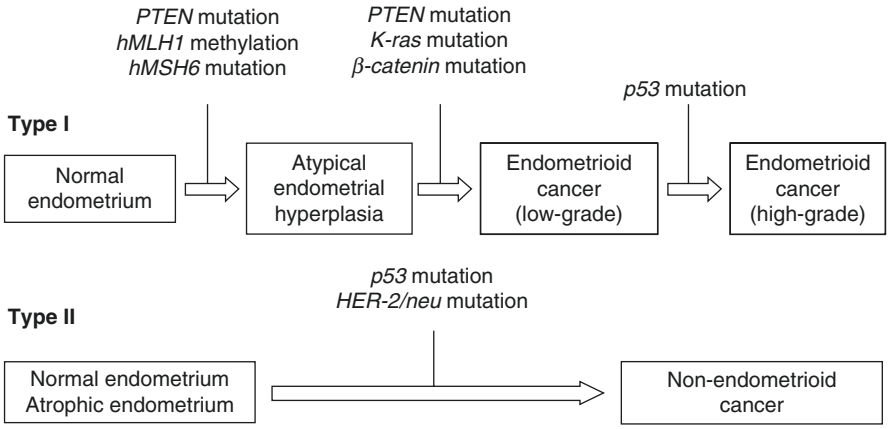


Fig. 2.1 Gene mutations in the carcinogenesis of endometrial cancer

PTEN Mutation: PTEN gene is a tumor suppressor gene on chromosome 10 and encodes a lipid phosphatase which acts to maintain G1 arrest and enables apoptosis through an Akt-dependent mechanism (Akt is a serine/threonine-specific protein kinase which plays a key role in apoptosis, cell proliferation, and transcription) [33, 34]. Mutations in the PTEN tumor suppressor gene can be deletions, insertions, nonsense mutations, or missense mutations. Mutation, or deletions resulting in loss of heterozygosity (LOH) at chromosome 10q23, are detected in 37–61% of cancers [35]. The pattern of PTEN mutation is different in MSI and microsatellite stable cancers. MSI-positive tumors have a higher frequency of deletions involving three base pairs when compared with the MSI-negative group.

PTEN acts in opposition to phosphatidylinositol-3-kinase (PIK3CA) to control levels of phosphorylated Akt. These mutations of PTEN lead to increased activity of PI3 kinase with resultant phosphorylation of Akt and are found in 20% of endometrial hyperplasia, suggesting an early event in the development of type I cancer [36]. These mutations in endometrial cancers are associated with endometrioid histology, early-stage and favorable prognosis (in contrast to TP53 mutations).

APC mutation: *APC* is also a tumor suppressor gene and APC protein induces degradation of β-catenin, a Wnt-signaling factor. Aberrant *APC* methylation is found in endometrial hyperplasia and early endometrial cancer (EEC). Ignatov et al. showed that *APC* methylation may be an important marker of early carcinogenesis of endometrial cancer [37].

ARID1A gene: Mutation of the ARID1A gene and loss of the corresponding protein BAF250a has recently been described in 29% of grade 1 or 2 and 39% of grade 3 EEC, 18% of uterine serous carcinomas and 26% of uterine clear cell carcinomas. Uterine low-grade EEC has also shown a relatively high-frequency loss of ARID1A expression (26%) and ARID1A mutations (40%) [38, 39].

Different tumor suppressor genes affected in type I and type II of endometrial cancer are shown in Table 2.2 (Ref: TCGA Data portal) [7].

2.4.3.2 Oncogenes

β-Catenin (CTNNB1) mutation: β-catenin is a component of the E-cadherin-catenin unit essential for cell differentiation and maintenance of normal tissue architecture, and plays an important role in signal transduction. Increased nuclear levels of

Table 2.2 Tumor suppressor genes found in EC

Gene	Type I EC	Type II EC
TP53 mutation	15%	90%
FWXW7 mutation	10%	30%
PP2R1A mutation	Rare	25%
ARID1A mutation	40%	10%
PTEN mutation	80%	Rare
MLH1 methylation	35%	Rare
CTCF mutation	25%	Rare
POLE mutation	10%	Rare

β-catenin produce transcriptional activation through the LEF/Tcf pathway [40]. This is associated with increased invasiveness and metastatic potential and is an independent poor prognostic factor in stage IV endometrial cancer and recurrent endometrial cancer. β-catenin mutation is a pathway to endometrial carcinogenesis which is independent of PTEN [41, 42]. Although MSI, PTEN, and K-ras mutations frequently coexist with each other, these molecular abnormalities are not usually seen in tumors with β-catenin alterations [43]. β-Catenin changes are present in some premalignant lesions, suggesting that it is an early step of endometrial tumorigenesis that is clonally represented in all tumor cells. Mutation of β-catenin was found in 40% of type I endometrial cancers.

K-ras mutation: The *K-ras* oncogene encodes a protein which has a signaling function from activated membrane receptors in the MAPK pathway. K-ras mutations cause excess signalling leading to excessive cell proliferation and carcinogenesis. *K-ras* mutations have been detected in 6–16% of cases of endometrial hyperplasia [44] and 10–31% cases of endometrial cancer [45, 46]. *K-ras* is involved in two stages of carcinogenesis: a shift from endometrial hyperplasia to endometrial cancer and invasive proliferation of well-differentiated tumor cells. K-ras mutations are higher in well-differentiated cancers, especially type I.

HER-2/neu overexpression: HER-2/neu is a tyrosine kinase membrane receptor in the epidermal growth factor (EGF) receptor family and mutation of this oncogene leading to overexpression of HER-2/neu is more prevalent in serous endometrial cancer.

RB and cyclin: Non-phosphorylated RB protein inhibits cell proliferation in the G0 and early G1 phases. After phosphorylation by the complex of cyclin and cyclin-dependent kinase (CDK), pRB releases the transcription factor E2F, which then increases DNA polymerase activity and promotes cell proliferation. Cyclin is a protein that controls the cell cycle in cooperation with CDK and is overexpressed in endometrial cancer. Shih et al. [47] showed that expression of cyclin A was an independent poor prognostic factor.

FGFR2 gene: Activating mutation in Fibroblast Growth Factor 2 gene is found in 10% in endometrial cancers and is associated with worse disease-free interval and overall survival [48].

PIK3CA: Activating mutation in the catalytic subunit of PI3K (PIK3CA) leads to activation of Akt, which leads to upregulation of mTOR (mammalian target of Rapamycin), a key regulator of apoptosis and cellular growth. This mutation is found in 36% of endometrial cancers.

The oncogenes associated with type I and type II endometrial cancers are shown in Table 2.3.

2.4.4 MicroRNA

- MicroRNAs (miRNAs) are short noncoding RNAs of 18–25 base pairs that regulate gene expression.
- miRNAs that inhibit DNA methylation in cancers are referred to as tumor suppressor miRNAs and methylation of a tumor suppressor miRNA can lead to

Table 2.3 Oncogenes associated with EC

Gene	Type I EC	Type II EC
CTNNB1(β-*catenin*) mutation	40%	Rare
PIK3CA mutation	55%	40%
PIC3R1 mutation	40%	Rare
KRAS mutation	25%	Rare
HER-2/neu amplification	Rare	30%
FGFR2 mutation	15%	10%
MYC amplification	Rare	25%

oncogene activation. Dysregulation of microRNA is implicated in carcinogenesis by manipulation of cell growth and apoptosis.

- Huang et al. [49] showed that miR-129-2 functions as a tumor suppressor-miRNA through negative regulation of the oncogene SRY-related high-mobility group box 4 (SOX4), which is overexpressed in endometrial cancer.
- miR-152, which is a tumor suppressor miRNA, inhibits DNA methyltransferase 1 (DNMT1) as well as oncogenes like E2F3, MET, and Rictor. This property potentiates the use of miR-152 in the treatment of endometrial cancer [50].
- Fang et al. showed that expression of miRNA-93 in serum was significantly lower in patients with EC than healthy controls, and levels of miRNA significantly correlated with clinical stage and other pathological characteristics of EC (like lymph node metastasis) [51].
- MicroRNA-320a serves an antitumor role in EC through regulation of Insulin-like Growth Factor-1R and hence it can be used as the target for gene therapy of EC [52].

2.5 Cytogenetic Basis of Different Characteristics of EC

2.5.1 Myometrial Invasion

Epithelial-to-mesenchymal transition (EMT) is an important mechanism in invasion and metastasis. Different molecular and genetic alterations have been found to be associated with myometrial invasion:

- Increased expression of transcriptional repressors of E-cadherin, such as Snail and Twist, leads to decreased E-cadherin immunoreactivity which is found in metastatic EC [53].
- Increase in transcriptional factors such as SLUG, ZEB1, and HMGA2 mRNA expression in the myoinvasive EC [54].
- Upregulation of ERM/ETV5 (member of the Ets transcription factors) is associated with increased matrix metalloproteinase 2 (MMP 2) leading to myometrial invasion [55, 56].
- β-catenin nuclear accumulation resulting from CTNNB1 mutations leads to an increase in matrix metalloproteinase MMP 7.
- There is an upregulation of transcription factor RUNX1/AML1 during invasion [57].

2.5.2 Apoptosis Resistance

Development and progression of carcinoma depend on deregulation of apoptosis. Some molecular abnormalities detected in EC may be associated with apoptosis deregulation:

- Mutations in PTEN, which is very common in Type 1 EC, leads to constitutively active Akt, which suppresses apoptosis.
- Nuclear factor (NF)-kB activation also leads to activation of target genes such as FLIP and Bcl-XL which causes apoptosis resistance [58].
- One of the most important regulators of death receptor signaling is FLIP, which can be transcriptionally regulated by casein kinase-2 (CK2), a Ser/Thr kinase in EEC. FLIP regulation provides resistance to TRAIL-induced extrinsic apoptotic pathway [59].
- P53 alterations as well as increased expression of Bcl-2 resulting from exacerbated PI3K/AKT signaling cause an increase in apoptosis.
- There is upregulated Bcl-xL and Bcl-2 in EC compared with normal tissue and these are involved in the development of metastases.

2.5.3 Resistance to Ionizing Radiation Treatment

Surgery with adjuvant radiation is the treatment of choice of endometrial carcinoma. There are a number of cases which have resistance to radiation, and they subsequently manifest as postradiation recurrence. Understanding the molecular and genetic mechanism of radiation resistance can help in the management of EC by instituting a more targeted therapy.

Oxygen fixes the damage and enhances radiation-induced cell death by reacting with the radiation-created broken ends of DNA. This phenomenon is known as the oxygen enhancement effect. Tumor hypoxia renders a tumor resistant to radiotherapy both by the absence of this oxygen enhancing effect as well as by activation of some signalling pathways as enumerated below:

- MLH1 promoter methylation [60]
- Alterations in the P53-suppressor gene [61]
- Hypoxia-induced β-catenin nuclear translocation factors leading to increased expression of β-catenin [62]
- Hypoxic conditions leading to increased expression of HIF-1 alpha expression which activates the classical NF-kB pathway [63]

2.6 Conclusion

EC is the most common gynecological cancer and has a good prognosis when diagnosed early. The basic management is surgery in early stages. But adjuvant therapy is required for advanced stage and highergrade cancer. The genetic basis of the

disease is very complex and interdependent on different cytogenetic factors. It is important to understand the complexity of cytogenetics as it can help to optimize the management of EC.

Key Points Type I endometrial cancer is an estrogen-dependent tumor, but along with estrogen, different genetic as well as epigenetic changes or mutations are also involved in carcinogenesis.

- Endometrial cancer arises due to an imbalance between estrogen-induced endometrial proliferation and mismatch repair system. In premenopausal women, there is sufficient estrogen for cell growth without sufficient MMR activity leading to carcinogenesis. This intermediate period is referred to as the "cancer window" for endometrial carcinoma.
- There are different mechanisms involved in the genesis of EC at the cytogenetic level which involve epigenetics, abnormal mismatch repair system, and genetic mutations.
- Gene mutations can affect in two ways, either by inactivation of some tumor suppressor genes, or activation of some oncogenes. It also involves changes in microRNA.
- Due to involved complex genetics in EC, The Cancer Genome Atlas (TCGA) project has categorized endometrial cancer into four broad categories.
- Genetic basis of different characteristics such as myometrial invasion, apoptosis resistance, and resistance to ionizing radiation treatment of EC are different but they are interdependent.

References

1. Sorosky JI. Endometrial cancer. Obstet Gynecol. 2012;120:383–97.
2. Soslow RA. Endometrial carcinomas with ambiguous features. Semin Diagn Pathol. 2010;27:261–73.
3. TCGA. Data portal. http://tcga-data.nci.nih.gov/tcga.
4. Miyamoto T, Shiozawa T, Kashima H, et al. Estrogen up-regulates mismatch repair activity in normal and malignant endometrial glandular cells. Endocrinology. 2006;147:4863–70.
5. Wu H, Chen Y, Liang J, et al. Hypomethylation linked activation of PAX2 mediates tamoxifen-stimulated endometrial carcinogenesis. Nature. 2005;438:981–7.
6. Zhao Y, Yamashita T, Ishikawa M. Regulation of tumor invasion by HOXB13 gene overexpressed in human endometrial cancer. Oncol Rep. 2005;13:721–6.
7. Zukerberg LR, DeBernardo RL, Kirley SD, et al. Loss of cables, a cyclin-dependent kinase regulatory protein, is associated with the development of endometrial hyperplasia and endometrial cancer. Cancer Res. 2004;64:202–8.
8. Goldberg AD, Allis CD, Bernstein E. Epigenetics: a landscape takes shape. Cell. 2007;128:635–8.
9. Holliday R. The inheritance of epigenetic defects. Science. 1987;238:163–70.
10. Schofield PN, Joyce JA, Lam WK, et al. Genomic imprinting and cancer; new paradigms in the genetics of neoplasia. Toxicol Lett. 2001;120:151–60.
11. Ushijima T. Detection and interpretation of altered methylation patterns in cancer cells. Nat Rev Cancer. 2005;5:223–31.

12. Gal-Yam EN, Jeong S, Tanay A, Egger G, Lee AS, Jones PA. Constitutive nucleosome depletion and ordered factor assembly at the GRP78 promoter revealed by single molecule footprinting. PLoS Genet. 2006;2:160.
13. Appanah R, Dickerson DR, Goyal P, Groudine M, Lorincz MC. An unmethylated 3′ promoter-proximal region is required for efficient transcription initiation. PLoS Genet. 2007;3:27.
14. Kondo E, Furukawa T, Yoshinaga K, et al. Not hMSH2 but hMLH1 is frequently silenced by hypermethylation in endometrial cancer but rarely silenced in pancreatic cancer with microsatellite instability. Int J Oncol. 2000;17:535–41.
15. Muraki Y, Banno K, Yanokura M, et al. Epigenetic DNA hypermethylation: clinical applications in endometrial cancer. Oncol Rep. 2009;22:967–72.
16. Whitcomb BP, Mutch DG, Herzog TJ, Rader JS, Gibb RK, Goodfellow PJ. Frequent HOXA11 and THBS2 promoter methylation, and a methylator phenotype in endometrial adenocarcinoma. Clin Cancer Res. 2003;9:2277–87.
17. Zhang QY, Yi DQ, Zhou L, Zhang DH, Zhou TM. Status and significance of CpG island methylator phenotype in endometrial cancer. Gynecol Obstet Invest. 2011;72:183–91.
18. Weisenberger DJ, Siegmund KD, Campan M, et al. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. Nat Genet. 2006;38:787–93.
19. Marks P, Rifkind RA, Richon VM, Breslow R, Miller T, Kelly WK. Histone deacetylases and cancer: causes and therapies. Nat Rev Cancer. 2001;1:194–202.
20. Grozinger CM, Schreiber SL. Deacetylase enzymes: biological functions and the use of small-molecule inhibitors. Chem Biol. 2002;9:3–16.
21. Damaskos C, Garmpis N, Karatzas T, Nikolidakis L, Kostakis ID, Garmpi A, Karamaroudis S, Boutsikos G, Damaskou Z, Kostakis A, Kouraklis G. Histone deacetylase (hdac) inhibitors: current evidence for therapeutic activities in pancreatic cancer. Anticancer Res. 2015;35:3129–35.
22. Weichert W, Roske A, Niesporek S, Noske A, Buckendahl C, Dietel M, Boehm M, Beckers T, Denkert C. Class I histone deacetylase expression has independent prognostic impact in human colorectal cancer: specific role of class I histone deacetylases in vitro and in vivo. Clin Cancer Res. 2008;14:1669–77.
23. Uchida H, Maruyama T, Nagashima T, Asada H, Yoshimura Y. Histone deacetylase inhibitors induce differentiation of human endometrial adenocarcinoma cells through up-regulation of glycodelin. Endocrinology. 2005;146:5365–73.
24. Takai N, Ueda T, Nishida M, Nasu K, Narahara H. Anticancer activity of MS-275, a novel histone deacetylase inhibitor, against human endometrial cancer cells. Anticancer Res. 2006;26:939–45.
25. Ahn MY, Jung JH, Na YJ, Kim HS. A natural histone deacetylase inhibitor, Psammaplin A, induces cell cycle arrest and apoptosis in human endometrial cancer cells. Gynecol Oncol. 2008;108:27–33.
26. Fakhry H, Miyamoto T, Kashima H, Suzuki A, Ke H, Konishi I, Shiozawa T. Immunohistochemical detection of histone deacetylases in endometrial carcinoma: involvement of histone deacetylase 2 in the proliferation of endometrial carcinoma cells. Hum Pathol. 2010;41:848–58.
27. Peltomäki P, Vasen H. Mutations associated with HNPCC predisposition: update of ICG-HNPCC/INSiGHT mutation database. Dis Markers. 2004;20:269–76.
28. Schweizer P, Moisio AL, Kuismanen SA, et al. Lack of MSH2 and MSH6 characterizes endometrial but not colon carcinomas in hereditary nonpolyposis colorectal cancer. Cancer Res. 2001;61:2813–5.
29. Duggan BD, Felix JC, Muderspach LI, Tourgeman D, Zheng J, Shibata D. Microsatellite instability in sporadic endometrial carcinoma. J Natl Cancer Inst. 1994;86:1216–21.
30. Kohler MF, Berchuck A, Davidoff AM, et al. Overexpression and mutation of p53 in endometrial carcinoma. Cancer Res. 1992;52:1622–7.
31. Zheng W, Xiang L, Fadare O, Kong B. A proposed model for endometrial serous carcinogenesis. Am J Surg Pathol. 2011;35:e1–14.

32. Zhang X, Liang SX, Jia L, et al. Molecular identification of 'latent precancers' for endometrial serous carcinoma in benign-appearing endometrium. Am J Pathol. 2009;174:2000–6.
33. Kurose K, Zhou XP, Araki T, et al. Frequent loss of PTEN expression is linked to elevated phosphorylated Akt levels, but not associated with p27 and cyclin D1 expression, in primary epithelial ovarian carcinomas. Am J Pathol. 2001;158:2097–106.
34. Zhu X, Kwon CH, Schlosshauer PW, et al. PTEN induces G (1) cell cycle arrest and decreases cyclin D3 levels in endometrial carcinoma cells. Cancer Res. 2001;61:4569–75.
35. Mutter GL. PTEN, a protean tumor suppressor. Am J Pathol. 2001;158:1895–8.
36. Milner J, Ponder B, Hughes-Davies L, et al. Transcriptional activation functions in BRCA2. Nature. 1997;386:772–3.
37. Ignatov A, Bischoff J, Ignatov T, et al. APC promoter hypermethylation is an early event in endometrial tumorigenesis. Cancer Sci. 2010;101:321–7.
38. Guan B, Mao TL, Panuganti PK, Kuhn E, Kurman RJ, Maeda D, et al. Mutation and loss of expression of ARID1A in uterine low-grade endometrioid carcinoma. Am J Surg Pathol. 2011;35:625–32.
39. Wiegand KC, Lee AF, Al-Agha OM, Chow C, Kalloger SE, Scott DW, et al. Loss of BAF250a (ARID1A) is frequent in high-grade endometrial carcinomas. J Pathol. 2011;224:328–33.
40. Morin PJ, Sparks AB, Korinek V, et al. Activation of beta-catenin-Tcf signaling in colon cancer by mutations in beta-catenin or APC. Science. 1999;275:1787–90.
41. Su LK, Vogelstein B, Kinzler KW. Association of the APC tumor suppressor protein with catenins. Science. 1993;262:1734–7.
42. Rubinfeld B, Albert I, Porfiri E, et al. Binding of GSK3beta to the APC-beta-catenin complex and regulation of complex assembly. Science. 1996;272:1023–6.
43. Palacios J, Gamallo C. Mutations in the betacatenin gene (CTNNB1) in endometrioid ovarian carcinomas. Cancer Res. 1998;58:1344–7.
44. Sasaki H, Nishii H, Takahashi H, et al. Mutation of the Ki-rasproto oncogene in human endometrial hyperplasia and carcinoma. Cancer Res. 1993;53:1906–10.
45. 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;53:1883–8.
46. Caduff RF, Johnston CM, Frank TS. Mutations of the Ki-ras oncogene in carcinoma of the endometrium. Am J Pathol. 1995;146:182–8.
47. Shih HC, Shiozawa T, Kato K, et al. Immunohistochemical expression of cyclins, cyclin-dependent kinases, tumor suppressor gene products, Ki-67, and sex steroid receptors in endometrial carcinoma: positive staining for cyclin A as a poor prognostic indicator. Hum Pathol. 2003;34:471–8.
48. Pollock PM, Gartside MG, Dejaza LC, et al. Frequent activating FGFR2 mutations in endometrial carcinomas parallel germline mutations associated with craniosynostosis and skeletal dysplasia syndromes. Oncogene. 2007;26:7158–62.
49. Huang YW, Liu JC, Deatherage DE, et al. Epigenetic repression of microRNA-129-2 leads to overexpression of SOX4 oncogene in endometrial cancer. Cancer Res. 2009;69:9038–46.
50. Tsuruta T, Kozaki K, Uesugi A, et al. miR-152 is a tumor suppressor microRNA that is silenced by DNA hypermethylation in endometrial cancer. Cancer Res. 2011;71:6450–62.
51. Fang S, Gao M, Xiong S, Chen Q, Zhang H. Expression of serum Hsa-miR-93 in uterine cancer and its clinical significance. Oncol Lett. 2018;15(6):9896–900.
52. Shu S, Liu X, Xu M, Gao X, Chen S, Zhang L, Li R. MicroRNA-320a acts as a tumor suppressor in endometrial carcinoma by targeting IGF-1R. Int J Mol Med. 2019;43:1505–12.
53. Blechschmidt K, Kremmer E, Hollweck R, Mylonas I, Hofler H, Kremer M, et al. The E-cadherin repressor snail plays a role in tumor progression of endometrioid adenocarcinomas. Diagn Mol Pathol. 2007;16:222–8.
54. Montserrat N, Mozos A, Llobet D, Dolcet X, Pons C, de Herreros AG, et al. Epithelial to mesenchymal transition in early stage endometrioid endometrial carcinoma. Hum Pathol. 2012;43:632–43.

55. Llaurado M, Abal M, Castellvi J, Cabrera S, Gil-Moreno A, Perez-Benavente A, et al. ETV5 transcription factor is overexpressed in ovarian cancer and regulates cell adhesion in ovarian cancer cells. Int J Cancer. 2011;130:1532–43.
56. Monge M, Colas E, Doll A, Gonzalez M, Gil-Moreno A, Planaguma J, et al. ERM/ETV5 up-regulation plays a role during myometrial infiltration through matrix metalloproteinase-2 activation in endometrial cancer. Cancer Res. 2007;67:6753–9.
57. Planaguma J, Liljestrom M, Alameda F, Butzow R, Virtanen I, Reventos J, et al. Matrix metalloproteinase-2 and matrix metalloproteinase-9 codistribute with transcription factors RUNX1/AML1 and ETV5/ERM at the invasive front of endometrial and ovarian carcinoma. Hum Pathol. 2011;42:57–67.
58. Pallares J, Martinez-Guitarte JL, Dolcet X, Llobet D, Rue M, Palacios J, et al. Abnormalities in NF-kB family and related proteins in endometrial carcinoma. A tissue microarray study. J Pathol. 2004;13:569–77.
59. Dolcet X, Llobet D, Pallares J, Rue M, Comella JX, Matias-Guiu X. FLIP is frequently expressed in endometrial carcinoma and has a role in resistance to TRAIL-induced apoptosis. Lab Invest. 2005;85:885–94.
60. Pijnenborg JM, Dam-de Veen GC, de Haan J, van Engeland M, Groothuis PG. Defective mismatch repair and the development of recurrent endometrial carcinoma. Gynecol Oncol. 2004;94:550–9.
61. Pijnenborg JM, van de Broek L, Dam de Veen GC, Roemen GM, de Haan J, van Engeland M, et al. TP53 overexpression in recurrent endometrial carcinoma. Gynecol Oncol. 2006;100:397–404.
62. Pijnenborg JM, Kisters N, van Engeland M, Dunselman GA, de Haan J, de Goeij AF, et al. APC, beta-catenin, and E-cadherin and the development of recurrent endometrial carcinoma. Int J Gynecol Cancer. 2004;14:947–56.
63. Yeramian A, Santacana M, Sorolla A, Llobet D, Encinas M, Velasco A, et al. Nuclear factor beta/p100 promotes endometrial carcinoma cell survival under hypoxia in a HIF-1alpha in an independent manner. Lab Invest. 2011;91:859–71.

Endometrial Precancers: Diagnosis and Management

3

Anshuja Singla and Ritisha Basu

3.1 Introduction

Endometrial hyperplasia is defined as an irregular proliferation of the endometrial glands with an increase in the gland-to-stroma ratio [1]. Subclassification is based on the complexity of the glands and the presence of cytological atypia, if any. Normal menstrual cycle is a complex mix of interactions between estrogen and progesterone supplemented by the effect of age. A slight disturbance in this equilibrium leads to unopposed estrogen exposure and in turn endometrial abnormalities [2–4]. Postmenopausal estrogen–progesterone trial (PEPI trial) corroborated the fact that women exposed to estrogen-only hormones were more likely to develop endometrial hyperplasia than the placebo-treated women [5].

Abnormal uterine bleeding is usually the primary complaint and may include menorrhagia, intermenstrual bleeding, postmenopausal bleeding, and irregular bleeding on hormone replacement therapy or tamoxifen. Approximately 70% of women with abnormal uterine bleeding are diagnosed with benign findings and 15% are diagnosed with malignancy. The remaining 15% is the diagnosis of endometrial hyperplasia (EH), which includes a wide variety of lesions ranging from mild, reversible proliferations to the immediate precursors of carcinoma [6].

The current estimated incidence of EH in developed countries is around 2 lakh new cases in a year [7]. The peak incidence of endometrial hyperplasia without atypia (simple hyperplasia—142/lakh, complex—213/lakh women years) is noticed in the early 50s with atypia (56/lakh women years) being more common in the sixth decade [8]. The natural course and long-term follow-up is not a possibility with this condition as a majority of women are symptomatic and require immediate treatment.

A. Singla (✉) · R. Basu
Department of Obstetrics and Gynaecology, University College of Medical Sciencesand Guru Teg Bahadur Hospital, Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_3

3.2 Etiology

Estrogen stimulates endometrial proliferation by binding to estrogen receptors (ER) in endometrial cells. A relative excess of estrogen either endogenous or exogenous is one of the primary etiological factors in both endometrial hyperplasia and endometrial carcinoma [8, 9]. Notably, type 2 endometrial carcinoma do not arise in the backdrop of endometrial hyperplasia.

Obesity Obesity, especially BMI > 30 has almost a fourfold incidence of hyperplasia with atypia, since there is an unregulated conversion of androgen to estrogen in the peripheral adipose tissue and obesity also decreases the sex hormone binding globulin (SHBG) levels [10], thus increasing the free androgen levels for increased conversion to estrogen.

Nulliparity Nulliparity exposes a woman to more number of ovulatory cycles and in turn increasing estrogen exposure. Giving birth to a child decreases the risk of endometrial hyperplasia and this was most appreciated with females ≤52 years [11]. An inverse relationship with parity has been shown in other studies also [12].

PCOS PCOS women have a relative increase in estrogen-to-progesterone ratio, thus exposing the endometrium to increase in estrogenic environment and consequently increased chances of EH.

Genetics Genetic mutations like PTEN, Kras, PIK3CA, and MS1 have been observed in EH [2, 13].

Estrogen replacement therapy (ERT) ERT use in postmenopausal women without progestins increases the risk of EH which is dependent on the dose and duration with an approximate increase of tenfold for every decade of usage [2, 14, 15].

Infections and immunosuppression Bobrowska et al. found a high rate of EH (69% vs. 33%) in women who underwent renal transplantation versus controls [16].

Ovarian tumors Estrogen secreting ovarian tumors like granulosa cell tumors can be associated with EH in as high as 40% of cases.

3.3 Classification

Varying classification systems have been introduced since the entity of EH was established way back in 1963, but the most commonly used systems are by WHO and EIN system.

The histopathological assessment depends on nuclear, architectural, and cytological abnormalities. Further classification into simple and complex is based on the absence or presence of architectural abnormality and the crowding of the glandular framework [17].

In 1994, WHO came out with a classification system, wherein EH was subdivided into four categories: simple hyperplasia with and without atypia and complex hyperplasia with and without atypia. The year 2014 saw the dawn of the latest and the simplest classification wherein EH was divided into two categories—hyperplasia without atypia and hyperplasia with atypia (Fig. 3.1). Hyperplasia without atypia usually are benign changes and revert to normal if estrogenic endocrine environment returns to normal. In contrast, atypical hyperplasia has genetic and cellular expressions consistent with endometrial cancer. Risk of progression of various types of EH to endometrial carcinoma is shown in Table 3.1. This has particularly simplified the management part of EH since hyperplasia without atypia can be managed conservatively, but atypia essentially requires a radical surgical approach [2, 7, 18].

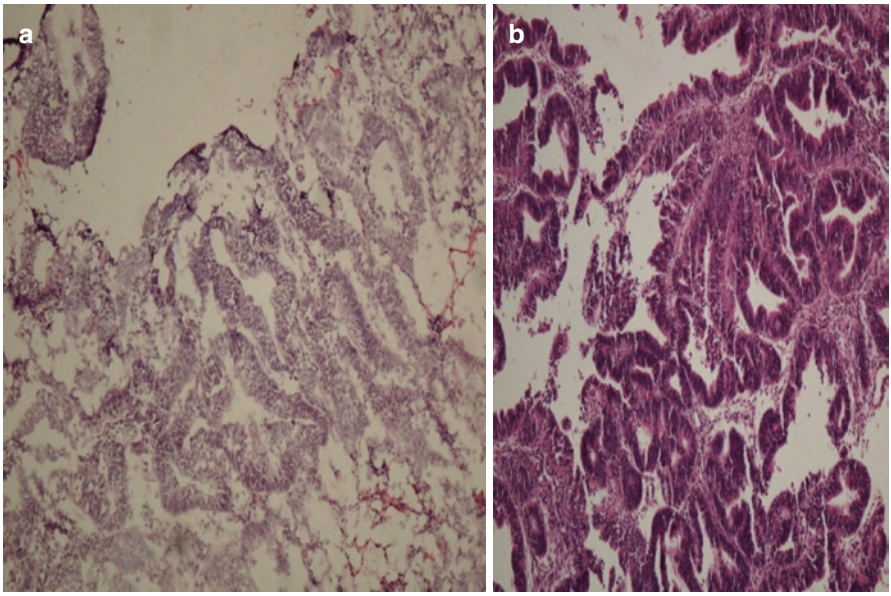


Fig. 3.1 Frozen section biopsy (**a**) and permanent histopathology (**b**) showing a cribriform pattern of multiple gland lumen suggestive of endometrial hyperplasia with atypia (100×)

Table 3.1 Risk of progression to cancer

Types	Progressing to cancer
Simple hyperplasia	1%
Complex hyperplasia	3%
Simple atypical hyperplasia	8%
Complex atypical hyperplasia	29%

3.3.1 Endometrial Intraepithelial Neoplasia

The International Endometrial Collaborative Group in 2000 recognized atypical endometrial hyperplasia as a premalignant lesion of the endometrium and redefined it as endometrial intraepithelial neoplasia (EIN), in congruence with the terminology used for cervical, vaginal, and vulval neoplastic lesions [19].

EIN is defined as "histological presentation of premalignant endometrial disease as identified by integrated molecular, genetic, histomorphometric and clinical outcome data." Endometrial intraepithelial neoplasia is diagnosed by the presence of cytological demarcation (≥1 mm lesion), crowded glandular architecture (area of gland more than area of stroma), and careful exclusion of mimics (polyps, secretory endometrium, and cancer) [20].

EIN system classifies hyperplasia into two groups—Benign and Endometrial Intraepithelial Neoplasia, based on five objective criteria that can be read on the conventional hematoxylin and eosin-stained sections by the practicing pathologist.

3.4 Comparison Between WHO and EIN Classification

Figure 3.2 illustrates the WHO and EIN classification system. The subcategories in both do not correspond directly but have some overlap. The 2014, fourth edition of "Tumors of Female Reproductive System" published by WHO endorses the EIN system [1]. ACOG committee opinion paper, 2015 favored the use of the EIN system over atypia [21]. EIN system offers a robust, reproducible classification method that correlates well with the progression of endometrial cancer, but has not gained acceptance, probably due to the lack of experience or the cost associated whereas the WHO system is widely accepted and used.

Comparison of the WHO and EIN classification systems for endometrial hyperplasia has, however, shown EIN to be superior in discriminating lesions with the highest risk of conversion to malignant disease.

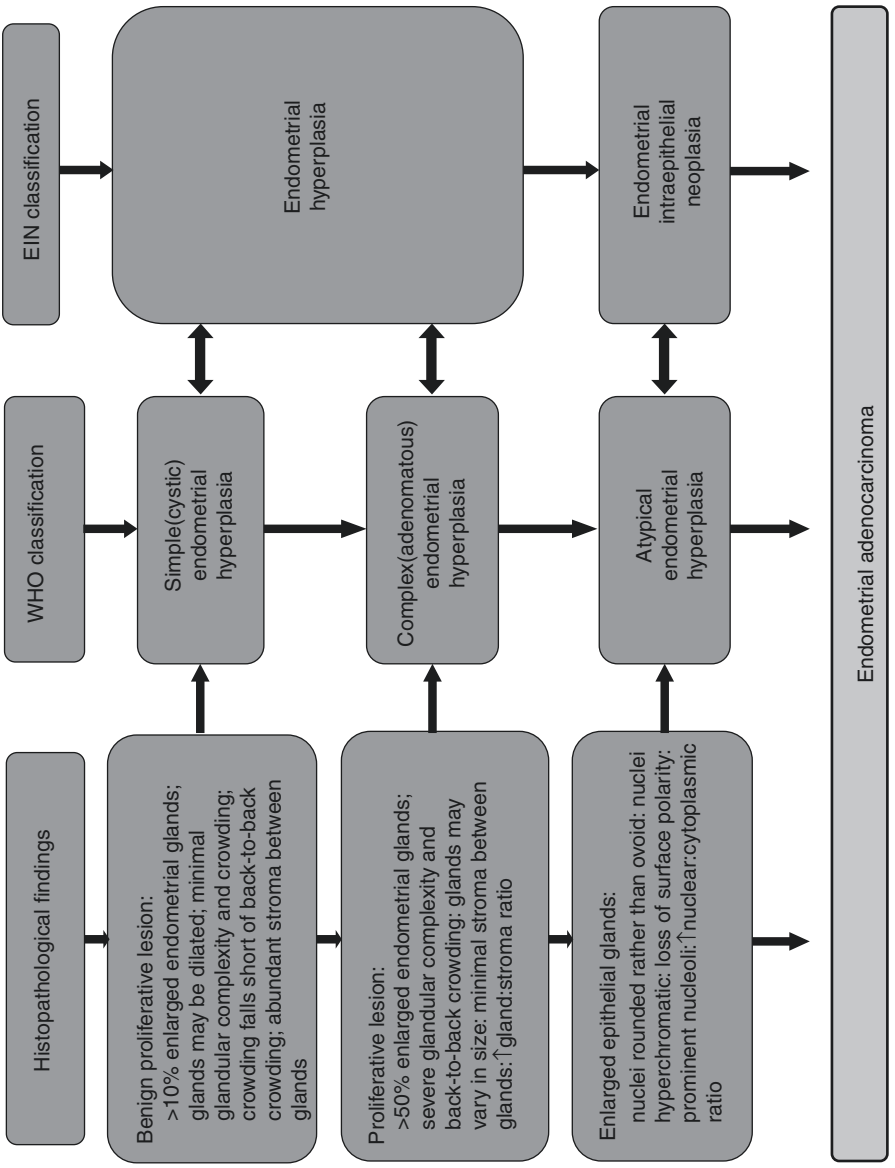


Fig. 3.2 Comparison of the WHO and EIN classification systems

3.5 Clinical Features

EH is essentially a biopsy diagnosis usually done for AUB presenting either with menorrhagia, intermenstrual bleeding, postmenopausal bleeding and irregular bleeding on hormone replacement therapy or tamoxifen. In an otherwise asymptomatic women, EH can be an incidental finding when cervical cytology demonstrates endometrial or abnormal glandular cells.

3.6 Diagnosis

Initial investigation of choice in women with AUB is a transvaginal ultrasound which may give a clue to the cause of AUB. Furthermore, since EH is a biopsy diagnosis, different techniques used to obtain the endometrial tissue include: office endometrial biopsy (EB), conventional D&C and hysteroscopy and biopsy.

3.6.1 Ultrasound

Transvaginal sonography (TVS) is the most common diagnostic method used for the evaluation of endometrium in women with AUB or postmenopausal bleeding (PMB). Various abnormalities which can be detected are irregular endometrium, double-layered ET, focal thickening, fibroids, and polyps. Various systematic reviews [22, 23] reported that in postmenopausal women an ET cutoff of 3 or 4 mm rules out EH and decreases the probability of cancer to <1%. A larger cutoff is recommended in women on HRT or tamoxifen who are either asymptomatic or have AUB [24].

The value of TVS appears to be limited in premenopausal women to the detection of structural abnormalities in the endometrium or an adnexal mass. In women with PCOS, a cutoff of 7 mm is recommended. A palpable adnexal mass with solid features of ultrasound may point to the possibility of granulosa cell tumor which has a 40% incidence of accompanying EH [24]. To conclude, ET of ≥4 mm after menopause in symptomatic women should be biopsied, though routine screening is only justified for Lynch syndrome families [25]. An inadequate biopsy in a symptomatic woman requires further evaluation, now by a hysteroscope and not a repeat blind office biopsy.

3.6.2 Office Endometrial Biopsy

Office EB with either pipelle, vabra aspirator, or gynosampler is safe and has high accuracy for diagnosis [3]. It may cause some discomfort and in 8% women biopsy is not possible due to cervical stenosis [26]. Pipelle has replaced the conventional D&C and even with a negative biopsy result, 2% women may still harbor hyperplasia [3]. The disadvantage with both the techniques is that they may not sample the

entire endometrial cavity especially if the endometrium is thin, or if there is a focal lesion like a polyp or there are submucosal uterine fibroids. Both the methods have been reported to have equal cancer detection rates in AUB women [14].

3.6.3 Hysteroscopy and Targeted Biopsy

Hysteroscopy is the investigation of choice in any patient who presents with postmenopausal bleeding, more so if the outpatient sampling fails or is inconclusive, if despite treatment AUB persists and if intrauterine structural problems like polyps, fibroids, etc. are suspected on ultrasound [14, 24] (Fig. 3.3). Office hysteroscopy is an outpatient procedure done with miniature hysteroscopes, without anesthesia and vaginal instrumentation. It has a very good sensitivity and specificity in detection of EH. A positive hysteroscopy result increases the probability of cancer to 72% from a pretest probability of 3.9% whereas a negative hysteroscopy decreases the probability of cancer to 0.6% [27].

3.6.4 CT/MRI/Biomarkers

There is insufficient evidence evaluating computed tomography (CT), diffusion-weighted magnetic resonance imaging (MRI), or biomarkers as aids in the management of endometrial hyperplasia and their use is not routinely recommended.

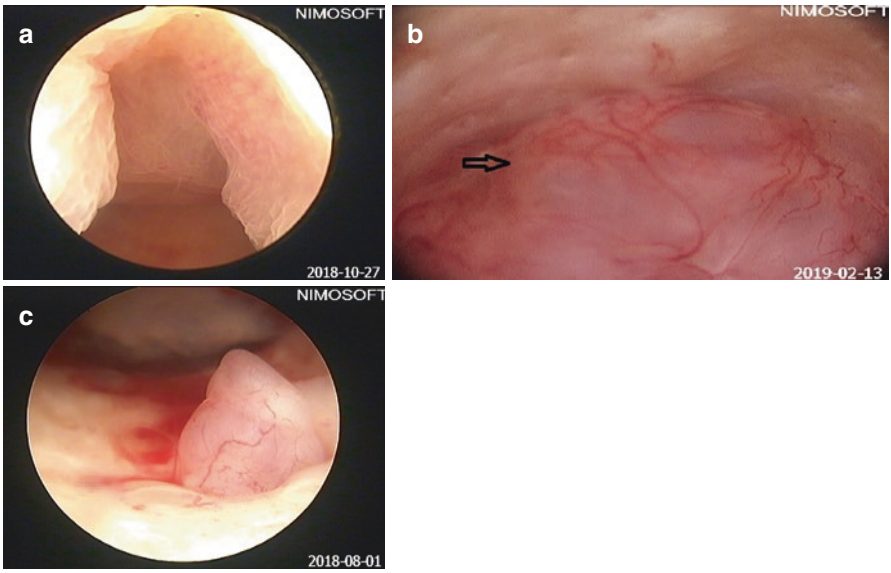


Fig. 3.3 (**a**) Hysteroscopic picture showing thickened endometrium. (**b**) Hysteroscopic picture showing submucosal fibroid. (**c**) Hysteroscopic picture showing endometrial polyp (benign)

3.7 Management

The management options offered depend on the woman's age, her general health, the desire for future fertility, the type of hyperplasia, and the risk factors for progression to cancer [28, 29]. Atypia and additional risk conferred by older age, obesity, and ovulatory dysfunction have to be kept in mind. Hyperplasia without atypia in younger women especially desirous of fertility can be managed conservatively, either by observation or progestin therapy which is not the case with atypia or symptomatic peri- and postmenopausal women [2].

Various treatment modalities include observation, medical management with drugs like progestin, aromatase and sulfatase inhibitors, selective estrogen receptor modulators (SERMS), metformin, Danazol, GnRH agonists and protein tyrosine kinase inhibitors (Genistein) and surgical management including hysterectomy [2, 30].

3.7.1 Observation

The risk of endometrial hyperplasia without atypia progressing to endometrial cancer is less than 5% over 20 years and the majority of cases of endometrial hyperplasia without atypia will regress spontaneously during follow-up. Observation alone with follow-up to ensure disease regression can be considered, especially when identifiable risk factors can be reversed.

Induction of ovulation in PCOS and attainment of menopause in perimenopausal women, change in dosage, duration or discontinuation of ERT and discontinuation of tamoxifen if possible, allows regression of EH. However, in symptomatic women with AUB where EH fails to regress after observation done for a year, may require progestin therapy [2].

3.7.2 Medical Management

3.7.2.1 Progestin

Progesterone mitigates the effects of estrogen and induces secretory changes in the endometrium. It causes the catabolism of estrogen receptors (ERs) and thus decreases estrogen dominance known to cause hyperplasia [31]. It also leads to apoptotic changes in the endometrial glands and inhibits myometrial angiogenesis leading to decidualization, thinning, and sloughing of the endometrium [30]. It has higher regression rates of 89–96% compared with observation alone (74–81%) [32]. Indications of progestins include EH without atypia, need for future fertility, and women who are unfit or refuse for surgery. Contraindications to progestin therapy include:

- Pregnancy
- Known or suspected progesterone receptors (PR) positive breast malignancy

- Undiagnosed vaginal bleeding
- Severe liver dysfunction and past or current thromboembolism [33]

Progestins can be given orally, parentally (IV/IM), and through an intrauterine system (IUS).

The right regimen with regards to dosage, duration, and posttreatment follow-up is still to be investigated [34], but continuous treatment appears to be more effective in inducing endometrial regression [24]. Commonly used progestins are medroxyprogesterone acetate (MPA) 10–20 mg/day, megestral acetate 20–40 mg/day, and norethisterone 10–15 mg/day [32]. Recently, levonorgestrel (LNG-IUS) has been used with better results. Oral progestins have compliance issues and adverse effects, so LNG-IUS has been used which is minimally absorbed systemically, ensures a better compliance, and provides contraception also. In the meta-analysis by Abu Hashim and colleagues, LNG-IUS was found to induce higher regression when compared to oral progesterone at 3, 6, 12, and 24 months and these women had less chances of hysterectomy at follow-up [35]. Treatment should continue for at least 6 months in EH without atypia and if treatment is tolerated and fertility is not an issue, LNG-IUS use should be continued for 5 years. Regression rates varied from 84 to 100% for LNG-IUS and 50–64% for oral MPA [36]. Thus, evidence suggests that treatment with progestogens should be for a minimum of 6 months.

Hysterectomy is indicated in women when:

1. Follow-up endometrial sampling shows atypical hyperplasia.
2. No regression of pathology despite 12 months of treatment.
3. Relapse of endometrial hyperplasia after completing progestogen treatment.
4. There is persistence of bleeding symptoms despite treatment.
5. Women noncompliant to endometrial surveillance or medical treatment.

Follow-up and endometrial biopsy should take into account the baseline cancer risk, the response, tolerance and compliance to treatment, any medical problems, presence of symptoms, and finally the wishes of the woman. Common side effects of progestins include edema, weight gain, headache, dizziness, nausea, vomiting, menstrual abnormalities, thrombophlebitis, occasional depression, and hypertension [26]. Resistance to therapy has been seen in 12–53% of women. Reasons reported are decreased levels or alterations in the regulatory function of progesterone receptors particularly PRB, downregulation of PR, paracrine effects, and activation of transforming growth factor (TGF) signaling pathway [30].

3.7.2.2 Clomiphene or Aromatase Inhibitors

Women with EH without atypia desirous of future fertility can undergo ovulation induction with clomiphene or aromatase inhibitor. Corpus luteum formation leads to an increase in progesterone exposure and thus regression of EH in a few women [33].

3.7.2.3 Metformin

In women with stigmata of metabolic syndrome, metformin can be of good help. It causes a decrease in insulin resistance, increase in PR expression, and decrease in body weight, thus decreasing the estrogenic predominance [37, 38].

3.7.2.4 GnRH Agonist

Suppression of hypothalamic–pituitary–ovarian (HPO) axis by GnRH agonists decreases estrogen production and is thus counterproductive on endometrial proliferation. In an intramuscular dose of 3.75 mg every month for 6 months, GnRH agonists hold promise as a new modality. However, a recurrence of 25% was observed within 16 months of completion of the treatment [39]. GnRH has been variedly combined with Tibolone [40] and LNG-IUS [33]. But further studies are required before it emerges as the first-line treatment for EH.

3.7.2.5 Danazol

Danazol is a synthetic androgen with its known hypoestrogenic and hypoandrogenic effects resulting in endometrial atrophy and has been well suggested as a treatment modality [41–43]. Danazol IUD seems to be the news around the corner [44], but the known androgenic side effects and the increased predisposition of ovarian cancer in women with endometriosis is a hindrance to its adoption as a first-line option [45].

3.7.2.6 Genistein

Genistein, an isoflavonoid obtained from soya, suppresses genes like ifos, cfun, interleukin1-α, and TNF-α. Bitto et al. in a randomized controlled trial reported an improvement in symptoms in 42% women treated with genistein aglycone for 6 months [46]. But the evidence is still wanted before genistein become available for treatment of EH.

3.8 Surgical

Surgical treatment includes hysterectomy with or without bilateral salpingo-oophorectomy (BSO). The preferable approach should be laparoscopic; however, abdominal and vaginal routes can also be used. Morcellation of the uterus should not be done due to the risk of dissemination of EC if coexistent. Gross inspection of the specimen as well as a frozen section in high-risk women should be done to rule out inadvertent EC. The benefit of doing a BSO should be weighed against the risks of premature menopause. If a decision is made to conserve the ovaries, bilateral salpingectomy should be done [24].

Endometrial ablation is not recommended for the treatment of EH/EIN. Post ablation, endometrial evaluation becomes difficult due to adhesion formation. Also complete and persistent destruction of endometrium cannot be ensured [24].

3.9 Management of Endometrial Hyperplasia Without Atypia

3.9.1 Premenopausal Women

In premenopausal women observation alone with follow-up ensures regression, if risk factors are reversed, failing which treatment with progestogens can be given.

LNG-IUS (Levonorgestrel intrauterine system) or continuous oral progestogen therapy (medroxyprogesterone 10–20 mg/day or norethisterone 10–15 mg/day) are accepted modalities for treatment [32, 47–49]. However, LNG-IUS has a higher disease regression rate and is associated with fewer adverse effects [35, 50]. Treatment should be for a minimum period of 6 months with a repeat endometrial sampling at 6 months to evaluate the regression of the pathology. At least two negative endometrial samplings at 6-months interval should be evidenced to document complete regression [51, 52]. In women at higher risk of relapse, once two consecutive negative endometrial biopsies at 6-months interval have been obtained, a long-term follow-up should be considered with annual endometrial biopsies till a definitive treatment is considered [53].

3.9.2 Postmenopausal

Bilateral salpingo-oophorectomy along with hysterectomy should be offered in postmenopausal women. If there is a contraindication or refusal for surgery, progestogens with adequate follow-up can be done.

3.10 Management of Endometrial Hyperplasia with Atypia

Women with atypical hyperplasia should undergo a total hysterectomy because of the risk of underlying malignancy or progression to cancer (Table 3.1). Intraoperative frozen section analysis of the endometrium or routine lymphadenectomy has no benefits [54–57].

3.11 Specific Considerations

3.11.1 Women Desirous of Fertility

Risks of underlying malignancy and subsequent progression to endometrial cancer should be counselled in women wishing to retain fertility. After ruling out invasive endometrial cancer or coexisting ovarian cancer, the LNG-IUS should be recommended, with oral progestogens as a second-best alternative. Routine endometrial

surveillance should be every 3 months until two consecutive negative biopsies are obtained [58]. Disease regression should be achieved on at least one endometrial sample before the woman attempts to conceive.

In asymptomatic women and with histological disease regression as evidenced by a minimum of two consecutive negative endometrial biopsies, long-term follow-up with endometrial biopsy every 6–12 months is recommended. Once fertility is no longer required, hysterectomy should be offered.

3.11.2 Tamoxifen and Endometrial Hyperplasia

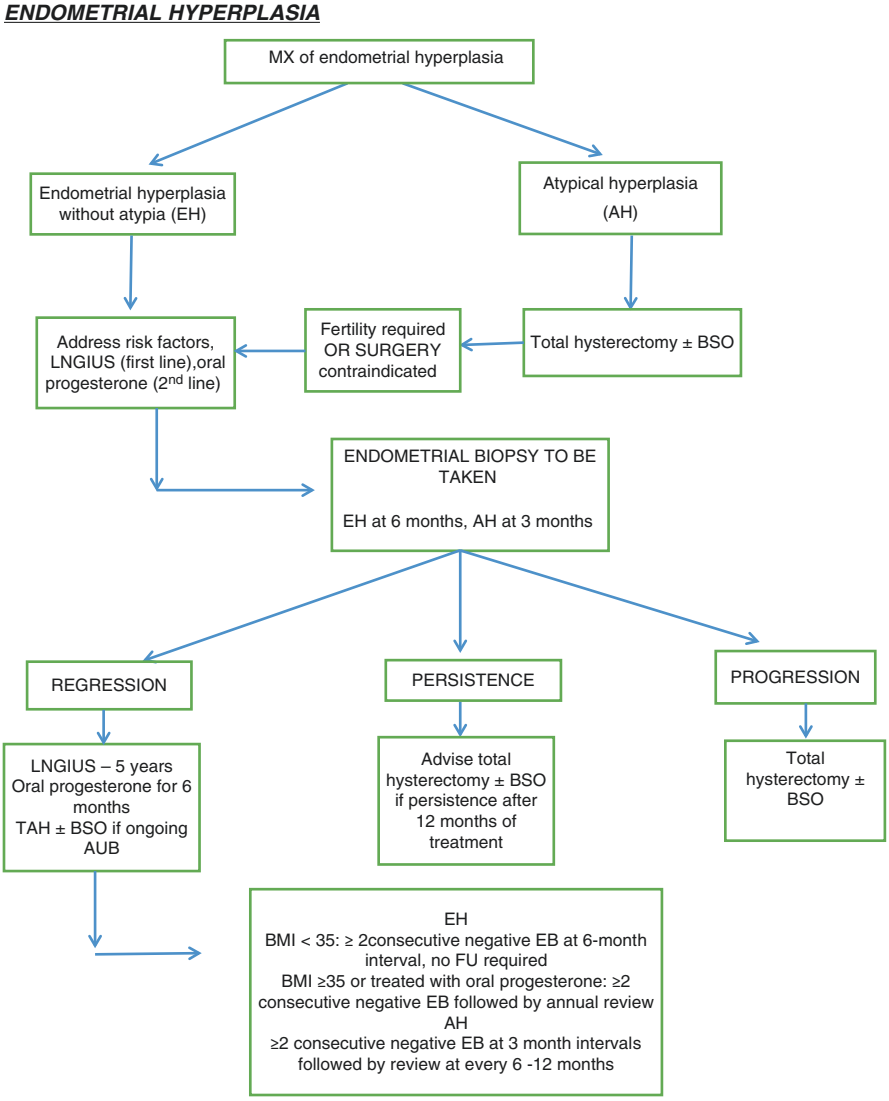
Tamoxifen, a SERM, has a competitive antagonistic action in breast and partial agonistic action in uterus. Used postoperatively in breast carcinoma, tamoxifen's estrogenic effect on uterus promotes the formation of fibroids, endometrial polyps, hyperplasia, and increased risk of endometrial cancer. Women taking this drug should be counselled about the risks and the need to avail medical help in case of abnormal vaginal bleeding [59]. There is evidence that LNG IUS reduces endometrial hyperplasia in women taking tamoxifen, but its uncertain risk on recurrence of breast cancer limits its routine use.

3.11.3 Use of Hormone Therapy in EH

Sequential hormone therapy (HT) should be changed to continuous combined (CC) or LNG-IUS should be considered (if EH occurs on CC, review the need of HT or replace it with LNG-IUS) [24].

3.12 Conclusion

Endometrial hyperplasia (EH) which encompasses a wide spectrum of endometrial patterns ranging from disordered proliferation to irregular proliferation of the endometrial glands is a known precursor for endometrial carcinoma (EC). Diagnosis of EH is important not only because of the symptoms caused by excessive estrogenic state but also because it precedes or is concurrently associated with endometrial cancer. The management of EH is guided by the age and future fertility desire of the woman as well as the histology of the hyperplasia. Hormonal treatment is the mainstay of management in hyperplasias which are not associated with atypia while hysterectomy is done in atypical hyperplasias.



Endometrial hyperplasia

Key points Endometrial hyperplasia is defined as an irregular proliferation of the endometrial glands with an increase in the gland-to-stroma ratio.

- The management options offered depend on the woman's age, her general health, the desire for future fertility, the type of hyperplasia, and the risk factors for progression to cancer.

- Endometrial hyperplasia without atypia responds well to progestins. But hysterectomy is the management for women with atypical hyperplasia.
- Hysteroscopy is the investigation of choice in any patient who presents with postmenopausal bleeding.
- Follow-up and endometrial biopsy should take into account the baseline cancer risk, the response, tolerance and compliance to treatment, any medical problems, presence of symptoms, and finally the wishes of the woman.

References

1. Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. WHO classification of tumours of female reproductive organs. 4th ed. Lyon: IARC; 2014.
2. Chandra V, Kim JJ, Benbrook DM, Dwivedi A, Rai R. Therapeutic options for management of endometrial hyperplasia. J Gynecol Oncol. 2016;27(1):1–25.
3. Landrum LM, Zuna RE, Walker JL. Endometrial hyperplasia, estrogen therapy, and the prevention of endometrial cancer. In: DiSaia PJ, Creasman WT, editors. Clinical gynecologic oncology. Philadelphia: Mosby Elsevier; 2007. p. 121–8.
4. Classification and diagnosis of endometrial hyperplasia [Internet]. Uptodate.com. 2017. https://www.uptodate.com/contents/classification-and-diagnosis-of-endometrial-hyperplasia?search=reed%20sd,urban%20r.%20r.%20classification%20and%20diagnosis%20of%20endometrial%20hyperplasia&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1. Accessed 19 Dec 2017.
5. Reed SD, Newton KM, Clinton WL, Epplein M, Garcia R, Allison K, Voigt LF, Weiss NS. Incidence of endometrial hyperplasia. Am J Obstet Gynecol. 2009;200(6):678.e1–6.
6. Lacey JV Jr, Chia VM. Endometrial hyperplasia and the risk of progression to carcinoma. Maturitas. 2009;63(1):39–44.
7. Sanderson PA, Critchley HOD, Williams ARW, Arends MJ, Saunders PTK. New concepts for an old problem: the diagnosis of endometrial hyperplasia. Hum Reprod Update. 2017;23(2):1–23.
8. Atunes CM, Strolley PD, Rosenshein NB, Davies JL, Tonascia JA, Brown C, et al. Endometrial cancer and estrogen use. Report of a large case-control study. N Engl J Med. 1979;300:9–13.
9. Montgomery BE, Daum GS, Dunton CJ. Endometrial hyperplasia: a review. Obstet Gynecol Surv. 2004;59:368–78.
10. Wise MR, Jordan V, Lagas A, Showell M, Wong N, Lensen S, et al. Obesity and endometrial hyperplasia and cancer in premenopausal women: a systematic review. Am J Obstet Gynecol. 2016;214:689–97.
11. Reed SD, Voigt LF, Newton KM, Holt VL, Weiss NS. Risk of complex and atypical endometrial hyperplasia in relation to anthropometric measures and reproductive history. Am J Epidemiol. 2008;168(6):563–70.
12. Brinton LA, Sakoda LC, Lissowska J, Sherman ME, Chatterjee N, Peplonska B, Szeszenia-Dabrowska N, Zatonski W, Garcia-Closas M. Reproductive risk factors for endometrial cancer among Polish women. Br J Cancer. 2007;96(9):1450–6.
13. Ricci E, Moroni S, Parazzini F, Surace M, Benzi G, Salerio B, et al. Risk factors for endometrial hyperplasia: results from a case-control study. Int J Gynecol Cancer. 2002;12:257–60.
14. Palmer JE, Perunovic B, Tidy JA. Review endometrial hyperplasia. Obstet Gynecol. 2008;10:211–6.
15. Wells M. Hyperplasias of the endometrium. In: Gershenson DM, McGuire WP, Gore M, Quinn MA, Gillian T, editors. Gynecologic cancer: controversies in management. Missouri: Elsevier Churchill Livingstone; 2004. p. 249–57.

16. Bobrowska K, Kamiński P, Cyganek A, Pietrzak B, Jabiry-Zieniewicz Z, Durlik M, Paczek L. High rate of endometrial hyperplasia in renal transplanted women. Transpl Proc. 2006;38(1):177–9.
17. Mazur MT. Endometrial hyperplasia/adenocarcinoma. a conventional approach. Ann Diagn Pathol. 2005;9(3):174–81.
18. Emons G, Beckmann M, Schmidt D, Mallmann P. New WHO classification of endometrial hyperplasias. Geburtshilfe Frauenheilkunde. 2015;75(02):135–6.
19. Mutter GL. Endometrial intraepithelial neoplasia (EIN): will it bring order to chaos? Endomet Collab Group Gynecol Oncol. 2000;76:287–90. https://doi.org/10.1006/gyno.1999.5580.
20. Sherman ME. Theories of endometrial carcinogenesis: a multidisciplinary approach. Mod Pathol. 2000;13:295–308. https://doi.org/10.1038/modpathol.3880051.
21. Parkash V, Fadare O, Tornos C, McCluggage WG. Committee Opinion No. 631: Endometrial intraepithelial neoplasia. Obstet Gynecol. 2015;126(4):897.
22. Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, Clark TJ, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol. 2010;116:160–7.
23. Gupta JK, Chien PF, Voit D, Clark TJ, Khan KS. Ultrasonographic endometrial thickness for diagnosing endometrial pathology in women with postmenopausal bleeding: a meta-analysis. Acta Obstet Gynecol Scand. 2002;81:799–816.
24. RCOG/BSGE Joint Guideline. Management of endometrial hyperplasia. Green-top Guideline No. 67, February 2016. https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg_67_endometrial_hyperplasia.pdf. Accessed 10 May 2019.
25. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Uterine neoplasms. https://www2.tri-kobe.org/nccn/guideline/gynecological/english/uterine.pdf. Accessed 5 May 2019.
26. Hacker NF, Friedlander ML. Uterine cancer. In: Berek JS, Hacker NF, editors. Berek & Hacker's gynecologic oncology. Philadelphia: Wolters Kluwer; 2015. p. 390–434.
27. Clark TJ, Voit D, Gupta JK, Hyde C, Song F, Khan KS. Accuracy of hysteroscopy in the diagnosis of endometrial cancer and hyperplasia: a systematic quantitative review. JAMA. 2002;288:1610–21.
28. Marsden DE, Hacker NF. Optimal management of endometrial hyperplasia. Best Pract Res Clin Obstet Gynaecol. 2001;15(3):393–405.
29. Iglesias DA, Huang M, Soliman PT, Djordjevic B, Lu KH. Endometrial hyperplasia and cancer. In: Karlan BY, Bristow RE, Li AJ, editors. Gynecologic oncology clinical practice & surgical atlas. New York: McGraw Hill; 2012. p. 250–326.
30. Trimble CL, Method M, Leitao M, Lu K, Ioffe O, Hampton M, et al. Management of endometrial precancers. Obstet Gynecol. 2012;120(5):1160–75.
31. Horn LC, Schnurrbusch U, Bilek K, Hentschel B, Einenkel J. Risk of progression in complex and atypical endometrial hyperplasia: clinicopathologic analysis in cases with and without progestogen treatment. Int J Gynecol Cancer. 2004;14:348–53.
32. Gallos ID, Shehmar M, Thangaratinam S, Papapostolou TK, Coomarasamy A, Gupta JK. Oral progestogens vs levonorgestrel-releasing intrauterine system for endometrial hyperplasia: a systematic review and meta-analysis. Am J Obstet Gynecol. 2010;203:547.e1–10.
33. Management of endometrial hyperplasia [Internet]. Uptodate.com. 2017. https://www.uptodate.com/contents/management-of-endometrial-hyperplasia?search=reed%20sd,urban%20r.%20r.%20classification%20and%20diagnosis%20of%20endometrial%20hyperplasia&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2. Accessed 19 Dec 2017.
34. Gunderson CC, Fader AN, Carson KA, Bristow RE. Oncologic and reproductive outcomes with progestin therapy in women with endometrial hyperplasia and grade 1 adenocarcinom: a systematic review. Gynecol Oncol. 2012;125:477–82.
35. Abu Hashim H, Ghayaty E, El Rakhawy M. Levonorgestrel releasing intrauterine system vs oral progestins for non-atypical endometrial hyperplasia: a systematic review and metaanalysis of randomized trials. Am J Obstet Gynecol. 2015;213:469–78.

36. Dolapcioglu K, Boz A, Baloglu A. The efficacy of intrauterine versus oral progestin for the treatment of endometrial hyperplasia. A prospective randomized comparative study. Clin Exp Obstet Gynecol. 2013;40:122–6.
37. Shao R, Li X, Feng Y, Lin JF, Billig H. Direct effects of metformin in the endometrium: a hypothetical mechanism for the treatment of women with PCOS and endometrial carcinoma. J Exp Clin Cancer Res. 2014;33:41.
38. Xie Y, Wang YL, Yu L, Hu Q, Ji L, Zhang Y, et al. Metformin promotes progesterone receptor expression via inhibition of mammalian target of rapamycin (mTOR) in endometrial cancer cells. J Steroid Biochem Mol Biol. 2011;126:113–20.
39. Agorastos T, Bontis J, Vakiani A, Vavilis D, Constantinidis T. Treatment of endometrial hyperplasias with gonadotropin-releasing hormone agonists: pathological, clinical, morphometric, and DNA-cytometric data. Gynecol Oncol. 1997;65:102–14.
40. Agorastos T, Vaitsi V, Paschopoulos M, Vakiani A, Zournatzi-Koiou V, Saravelos H, et al. Prolonged use of gonadotropin-releasing hormone agonist and tibolone as add-back therapy for the treatment of endometrial hyperplasia. Maturitas. 2004;48:125–32.
41. Sedati A, Mariani L, Giovinazzi R, Yacoub M, Atlante G. The effectiveness of danazol therapy in postmenopausal women affected by endometrial hyperplasia. Clin Exp Obstet Gynecol. 1992;19:161–5.
42. Mariani L, Sedati A, Giovinazzi R, Sindico R, Atlante G. Postmenopausal endometrial hyperplasia: role of danazol therapy. Int J Gynaecol Obstet. 1994;44:155–9.
43. Soh E, Sato K. Clinical effects of danazol on endometrial hyperplasia in menopausal and postmenopausal women. Cancer. 1990;66:983–8.
44. Tamaoka Y, Orikasa H, Sumi Y, Sakakura K, Kamei K, Nagatani M, et al. Treatment of endometrial hyperplasia with a danazol-releasing intrauterine device: a prospective study. Gynecol Obstet Invest. 2004;58:42–8.
45. Cottreau CM, Ness RB, Modugno F, Allen GO, Goodman MT. Endometriosis and its treatment with danazol or lupron in relation to ovarian cancer. Clin Cancer Res. 2003;9:5142–4.
46. Bitto A, Granese R, Triolo O, Villari D, Maisano D, Giordano D, et al. Genistein aglycone: a new therapeutic approach to reduce endometrial hyperplasia. Phytomedicine. 2010;17:844–50.
47. Gallos ID, Krishan P, Shehmar M, Ganesan R, Gupta JK. LNG-IUS versus oral progestogen treatment for endometrial hyperplasia: a long-term comparative cohort study. Hum Reprod. 2013;28:2966–71.
48. Ozdegirmenci O, Kayikcioglu F, Bozkurt U, Akgul MA, Haberal A. Comparison of the efficacy of three progestinsin the treatment of simple endometrial hyperplasia without atypia. Gynecol Obstet Invest. 2011;72:10–4.
49. Ørbo A, Vereide AB, Arnes M, Pettersen I, Straume B. Levon orgestrel-impregnated intrauterine device as treatment for endometrial hyperplasia: a national multicentre randomised trial. BJOG. 2014;121:477–86.
50. Abdelaziz AM, Abosrie M. Levonorgestrel-releasing intrauterine system is an efficient therapeutic modality for simple endometrial hyperplasia. J Am Sci. 2013;9:417–24.
51. Gallos ID, Ganesan R, Gupta JK. Prediction of regression and relapse of endometrial hyperplasia with conservative therapy. Obstet Gynecol. 2013;121:1165–71.
52. Scarselli G, Bargelli G, Taddei GL, Marchionni M, Peruzzi E, Pieralli A, et al. Levonorgestrel-releasing intrauterinesystem (LNG-IUS) as an effective treatment option for endometrial hyper plasia: a 15-year follow-up study. Fertil Steril. 2011;95:420–2.
53. Gallos ID, Krishan P, Shehmar M, Ganesan R, Gupta JK. Relapse of endometrial hyperplasia after conservative treatment: a cohort study with long-term follow-up. Hum Reprod. 2013;28:1231–6.
54. Edris F, Vilos GA, Al-Mubarak A, Ettler HC, Hollett-Caines J, Abu-Rafea B. Resectoscopic surgery may be an alternative to hysterectomy in high-risk women with atypical endometrial hyperplasia. J Minim Invasive Gynecol. 2007;14:68–73.
55. Indermaur MD, Shoup B, Tebes S, Lancaster JM. The accuracy of frozen pathology at time of hysterectomy in patients with complex atypical hyperplasia on preoperative biopsy. Am J Obstet Gynecol. 2007;196:e40–2.

56. Trimble CL, Kauderer J, Zaino R, Silverberg S, Lim PC, Burke JJ 2nd, et al. Concurrent endometrial carcinoma in women with a biopsy diagnosis of atypical endometrial hyperplasia: a Gynecologic Oncology Group study. Cancer. 2006;106:812–9.
57. American College of Obstetricians and Gynecologists, Society of Gynecologic Oncology. Practice Bulletin No. 149: Endometrial cancer. Obstet Gynecol. 2015;125:1006–26.
58. Park JY, Lee SH, Seong SJ, Kim DY, Kim TJ, Kim JW, et al. Progestin re-treatment in patients with recurrent endometrial adenocarcinoma after successful fertility sparing management using progestin. Gynecol Oncol. 2013;129:7–11.
59. Kedar RP, Bourne TH, Powles TJ, Collins WP, Ashley SE, Cosgrove DO, et al. Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomised breast cancer prevention trial. Lancet. 1994;343:1318–21.

Hereditary Endometrial Cancers

4

Nidhi Arora

4.1 Introduction

Cancer endometrium is currently the most common gynecological cancer in the developed world and is the second most common in the developing world. It is the 6th most commonly occurring cancer in women and the 15th most commonly occurring cancer overall [1]. The lifetime risk for endometrial cancer is 2–3% in the general population [2]. The various predisposing factors for endometrial cancer are hormone replacement therapy, exposure to tamoxifen, nulliparity, early menarche, late menopause, and obesity.

According to the histological classification, endometrial cancer is divided into two types: Type 1(80%)—low grade (1 and 2) with endometrioid histology, good prognosis, and estrogen dependent; type 2 (20%)—high-grade endometrioid and non-endometrioid tumors—serous, clear cell and others. These are independent of estrogen stimulation and are associated with poor prognosis.

Hereditary cancer syndrome is a genetic predisposition to certain types of cancer, often with onset at an early age, caused by inherited mutations in one or more genes. Endometrial cancer, despite being so commonly seen in women of reproductive age as well in the postmenopausal age group, it is not a sentinel cancer for the hereditary cancer syndromes. History of endometrial cancer in a first-degree relative has been considered an important risk factor; however, no specific genes have been identified other than those related to the hereditary cancer syndromes. A meta-analysis of 16 studies (including case–control and cohort) to estimate the risks associated with family history of endometrial cancer and cancer at other sites concluded that the collective risk of endometrial cancer up to age 70 years in females with a first-degree relative with endometrial cancer was 3.1% compared with <2% in the general population and the population-attributable risk was 3.5% (95% CI 2.8–4.2) [3].

N. Arora (✉)
Fetal Medicine, Madhukar Rainbow Children's Hospital, New Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_4

The various inheritable common causes of EC are mentioned in Table 4.1. Other rare causes can be the Li–Fraumeni syndrome, Cowden-like syndrome, and various SNPs. Overall, Lynch syndrome is the most common inheritable cancer syndrome associated with EC [10]. It accounts for around 2–5% of all endometrial cancers [11, 12]. Cowden syndrome, though rare, is associated with an increased risk of EC. With the development of whole-genome sequencing and the availability of multiple gene panel testing on the tumor tissue, many pathological gene variables are currently being studied for endometrial cancer. A novel classification based on the molecular analysis, EC is broadly divided into four groups—POLE-ultra mutated, microsatellite instability (MSI)-hypermutated, copy-number low, and copy-number high [13].

Germline mutations in POLD1 gene and the role of genetic polymorphisms in endometrial cancer are currently being studied by various authors. There are inconclusive reports on the role of BRCA mutations in the etiology of endometrial cancer.

4.2 Lynch Syndrome (LS)/Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

This is an autosomal dominant syndrome that affects multiple organs, predominantly colon and endometrium, others being gastric, ovary, small intestine, hepatobiliary, brain, and skin (Table 4.2). It is one of the most prevailing hereditary cancer syndromes with an estimated population incidence of 1:370 [18]. It is caused by a germline mutation in one of the alleles of the DNA mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2* (Table 4.1). It can also be due to large deletions in the *EPCAM* gene (present upstream) that causes epigenetic silencing of the adjacent MSH2 gene [19].

By convention, Lynch syndrome is referred to patients (along with the family tested) with inherited defects in the DNA mismatch repair genes whereas the term Hereditary nonpolyposis colorectal cancer (HNPCC) is for the patients and/or families who fulfil the Amsterdam criteria (Table 4.3).

The eponym "Lynch syndrome" recognizes Dr. Henry T. Lynch, the first author on the original 1966 publication that comprehensively described this condition [21]. Altogether, women with LS syndrome have a 60% lifetime risk of EC [22]. Women with LS who are affected both by colorectal and endometrial cancer, about 50% present first with endometrial cancer [23].

Out of all, mutations in MSH2 or MLH1 account for around 90% of the heterozygous germline mutations that have been associated in patients with Lynch syndrome (Table 4.2). Of the two, MSH2 mutations are seen more frequently and have been reported in approximately 50–66% of endometrial cancers with mutations. Mutations in MLH1 have been reported in around 24–40%, and MSH6 in 10–13% of cases. EPCAM gene deletions have a risk of developing endometrial cancer by up to 12% [24]. The PMS2 mutations are seen in very few individuals with LS.

Table 4.1 Known causes of hereditary endometrial cancer

Genetic syndrome	Gene	Risk of endometrial cancer	Other associated cancers	Clinical management	Age at diagnosis
Lynch syndrome [4, 5]	MLH1, MSH2, MSH6, PMS2, EPCAM del.	27–71%, high risk	Colorectal (52–82%), gastric (6–13%) ovary (4–12%), small bowel, hepatobiliary, brain, skin	• Colonoscopy/ polypectomy • Gynecological screening • Risk-reducing hysterectomy and salpingo-oophorectomy • Endoscopy	
Cowden syndrome [6, 7]	PTEN	19–28%, high risk	Thyroid, breast, colorectal	• Endometrial screening • Risk-reducing hysterectomy • Mammography • Possibly risk-reducing mastectomy • Examination of the thyroid • Colonoscopy/ polypectomy	
Peutz–Jeghers syndrome [4]	STK11/ LKB1	9%	Colorectal, pancreatic, breast, ovarian, other	• Mammography, breast magnetic resonance imaging • Risk-reducing medication • Risk-reducing mastectomy • Risk-reducing salpingo-oophorectomy	
Hereditary breast–ovarian cancer syndrome [8]	BRCA1, BRCA2	Unproven, likely modest risk (twofold)	Breast, ovary, prostate, pancreas, peritoneum, melanoma	• Mammography, MRI breast • Risk-reducing medication • Risk-reducing mastectomy • Risk-reducing salpingo-oophorectomy	
Polymerase proofreading associated polyposis [9]	POLD1, POLE	Unknown moderate/ high risk	Colorectal, gastric, various other	No consensus guidelines at present: • Colonoscopy/ polypectomy • Endoscopy • Endometrial screening	

Table 4.2 The various genotypes of Lynch syndrome and their lifetime cancer risks [14–17]

Lynch mutation	MLH1 (mut L homolog1) at chr. 3p22.2		MSH2 (mut S homolog 2) at chr. 2p21–16		MSH6 (mut S homolog 6) at chr. 2p16.3		PMS2 (postmeiotic segregation 2) at chr. 7p22.1	
Cancer site	Men	Women	Men	Women	Men	Women	Men	Women
Any Lynch cancer	59%	80%	71%	75%	31%	71%	–	–
Colorectal	34–47%	36–45%	37–47%	33–37%1	14–22%	10–26%	19–20%	11–15%
Endometrial	NA	18–54%	NA	21–51%	NA	16–49%	NA	12–24%
Ovarian	NA	11–20%	NA	15%	NA	1%	NA	–
Urinary tract	1.2%	3%	8%	10%	0.7%		–	
Gastric	20%	8%	2%	9%	–		–	
Small bowel	0.4%		1.1%		–		–	
Biliary/ pancreatic	1.9%		0.02%		–		–	
Brain tumors (Gliomas)	1.7%		2.5%		–		–	

Table 4.3 Amsterdam II Criteria [20]

1.	Presence of a minimum of 3 relatives with any Lynch syndrome-associated cancers (colorectal, endometrial, ovary, gastric, small bowel, ureter, renal pelvis).
2.	One of the relatives diagnosed should be a first-degree relative of the other two relatives.
3.	At least two successive generations should be affected.
4.	Familial adenomatous polyposis should be excluded if there is a colorectal cancer.
5.	There should be a pathological diagnosis of the tumors.

The *Mismatch Repair (MMR) system* acts as a proofreader of the genome and helps in its stability. It corrects the mismatches that occur in nucleotide pairs during DNA replication. Any defect in this process increases the rate of somatic mutations which act as a promoter of carcinogenesis [25].

Microsatellite instability (MSI) results from a deficiency in the MMR system. Microsatellites are widely distributed repetitive DNA sequences that are formed of short, tandemly repeated nucleotide motifs. When there is a deficiency in the MMR system, the microsatellites cause genomic instability with a gain or a loss of one or more units at numerous independent loci, thereby resulting in tumor formation [26, 27].

Studies have reported that MMR gene defects are not exclusive to Lynch syndrome and are seen in sporadic cancers as well [28–31]. In 15–25% of sporadic endometrial cancers, MSI positivity is noted and Lynch syndrome accounts for less than 5% of these endometrial cancers [32, 33]. When seen in sporadic form, the microsatellite instability is seen because of hypermethylation of the MLH1 gene promoter, leading to gene silencing. Sometimes, it is because of somatic mutations in the MSH6 gene.

4.2.1 Clinical Features

The main features attributable to endometrial cancer associated with Lynch syndrome are its early age of onset and its association with other cancers. Women with Lynch syndrome present with endometrial cancer at an earlier age (mean age 46–54 years) in comparison to the general population (mean age 60 years) [34–37].

It is unclear whether the hormonal risk factors increase the risk of EC in these women. Earlier, Balmana et al. (2006) reported that factors like obesity, diabetes mellitus, and prolonged estrogenic stimulation do not increase the risk of endometrial cancer in women with LS [38]. A recent, multicenter, retrospective cohort study analyzed the association of hormonal risk factors and endometrial cancer risk. Out of the 1128 women with a mismatch repair (MMR) gene mutation enrolled from Colon Cancer Family Registry, 133 women developed endometrial cancer. It was reported that later age at menarche (≥13 years), higher parity (≥1 live birth), and longer use of hormonal contraceptives (≥1 year) were associated with lower risk of endometrial cancer [39]. A prospective multicenter randomized controlled trial studied the effect of oral contraceptives and depo-medroxyprogesterone acetate on endometrial proliferation in women with Lynch syndrome. Both depo-MPA and OCP showed good response with a decrease in endometrial proliferation along with the microscopic changes in the endometrium that are characteristic of progestin action. Both these studies show that these women can be counselled in a similar way about the risks of endometrial cancer as the general population [40].

The risk of developing endometrial cancer in women with LS who presented first with colorectal cancer (CRC) was estimated to be 26% within 10 years of the initial CRC diagnosis [41]. They can present with synchronous or metachronous ovarian cancer [42]. Most of the women present with endometrial cancer at an early stage and thereby have a good prognosis [35, 36]. Boks et al. studied the survival in women with endometrial cancer with LS versus age-matched controls and concluded that the 5-year survival is similar in both the groups [35].

The histology of endometrial cancers associated with LS is heterogeneous, and it can present with both types of endometrial cancers (endometroid and non-endometroid). It was earlier thought that the individuals with pathogenic MMR gene variable develop the non-endometrioid type of cancer, but recent large population-based studies have not supported this hypothesis [37, 43].

Most of them are poorly differentiated and can be with mucinous, signet ring cell, or medullary differentiation. These histological features are also seen in colorectal tumors. There is the presence of infiltrating lymphocytes within the tumor along with the inflammatory infiltrate at the front of the tumor or the periphery. These are usually seen involving the lower uterine segment (LUS) [44].

In a study by Westin et al. [45], it was reported that the cancer involving the LUS is seen more in women with LS as compared to the general endometrial cancer patient population (29% and 1.8%, respectively).

4.2.2 Identification of Individuals at Risk for Lynch Syndrome

Defective MMR genes have been reported to be seen in around 1 out of 3100 individuals between the ages of 15 and 74 years [33]. Over the years, the strategies for identifying a person at risk of Lynch syndrome have evolved from the family history-based strategies to the tumor testing-based strategies. Once the patient is identified to be at risk, the genetic testing is performed.

4.2.2.1 Family History-Based Strategies

The most initial one was the Amsterdam criteria. Amsterdam I criteria require the presence of family history of three CRCs affecting two successive generations in which one of them is at an early age of less than 50 years. It was modified further to include along with the colorectal cancer, the other Lynch-associated malignancies and is described as the Amsterdam II criteria (Table 4.3) [20]. The Amsterdam criteria have a lower sensitivity (28–45%) but have a higher specificity (99%) [46]. With the knowledge that these tumors are characterized by microsatellite instability (MSI), tumor testing for MSI and immunohistochemistry assessment of the MMR proteins was performed as a first step to restrict genetic testing to only those who show deficient MMR status on other testing [47].

Thereby, Bethesda guidelines and its modification (Table 4.4) were developed to identify patients with CRC who should undergo tumor testing for microsatellite instability (MSI) [48]. In comparison to the Amsterdam criteria, the Bethesda criteria have a higher sensitivity (73–91%), but a lower specificity (62–77%) [46].

Several authors have analyzed targeted screening of women diagnosed with endometrial cancer using relevant clinical and histopathological features, i.e., young age at the time of diagnosis (less than 50 years), history of LS-associated synchronous or metachronous tumors in self or family, endometrial tumors restricted to LUS, and those presenting with the characteristic histology [44, 49–51].

Goodfellow et al. [52], in a study of 1002 patients, reported that 24% of patients with MMR mutations are older than 60 years and Mills et al. [53] reported that 75%

Table 4.4 Revised Bethesda guidelines for testing colorectal cancers with MSI [48]

1.	Diagnosis of colorectal cancer in patients under 50 years of age
2.	Existence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, regardless of age
3.	Colorectal cancer with the MSI-H-like histology diagnosed in a patient who is less than 60 years of age
4.	Colorectal cancer diagnosed in a patient with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers diagnosed at less than 50 years of age
5.	Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related tumor, irrespective of the age

of women with EC with MMR mutations were more than 50 years old and about that 85% of women had no history of any malignancy prior. Altogether, around 40% of patients with LS-associated germline MMR mutations had no common risk factors that could direct to further testing. Thereby, these clinical and histological features cannot be completely reliable to screen women for genetic testing. Also, the sensitivity and specificity of the Amsterdam and the revised Bethesda guidelines to predict endometrial cancer has not been studied well [54]. Moreover, these are imperfect and can miss up to 30% of LS-associated endometrial cancers [37].

Prediction Models

Several online prediction models [38, 55–57] have come up which use family history and the other clinical information to estimate the likelihood of carrying an LS gene mutation. The various prediction models are the MMRpredict, the MMRpro, and the PREMM model. Among these, the MMRpro (MLH1, MSH2, and MSH6 mutation) and the PREMM (MLH1 and MSH2 mutations) models can be used for women with EC. Since these two can predict only for the specific mutations mentioned, they still can miss the other mutations [58, 59]. The calculators for these models are available online.

4.2.2.2 Tumor-Based Strategies

Tumor specimens are tested for deficiency of DNA mismatch repair system to identify individuals with LS.

Microsatellite Instability (MSI) Testing

In a tumor specimen, the nucleotide repeat sequences are first amplified using Polymerase chain reaction (PCR). As mentioned above in the chapter, due to a defective DNA repair system, there is a loss or gain in these repetitive nucleotide sequences (microsatellites) thereby resulting in instability. Different panels are available to test these sequences. When >/=30% of the markers show expansion or contraction of the microsatellite region in the tumor in comparison to the normal tissue in the same patient, it is reported to have a high level of MSI (MSI-H). MSI-H tumors are usually non-colorectal/non-endometrial LS associated solid malignancies [60, 61]. MSI testing sensitivity and specificity depends on the mutations involved. It is 80–91% sensitive and 90% specific for MLH1 or MSH2 mutations, 55–77% sensitive and 90% specific for MSH6 or PMS2 mutations [62].

4.2.3 Immunohistochemistry (IHC)

A deficient DNA MMR system results in abnormal and deficient MMR protein (MLH1, PMS2, MSH2, and MSH6) synthesis. IHC staining identifies them as a loss of these proteins in the tumor specimen. The interpretation of this varies depending

upon the defective protein involved. It is 83% sensitive and 89% specific, irrespective of the type of MMR gene mutation involved [62].

Both these laboratory methods do result in improving the identification of patients with LS. The detection rate improves to 94% concordance with these methods in comparison to the detection rates of less than 50% using clinical screening methods alone [53, 63, 64]. When both compared, IHC staining is applicable to all mutations, it is less expensive, fast to perform than MSI testing, and is easier to be used on biopsy specimens [65]. However, even IHC staining is at times difficult to interpret due to the presence of insufficient tissue and is also costly to be performed on all newly diagnosed endometrial cancer [53, 66–68]. Since, most of endometrial cancer are not MSI-H tumors, it cannot be used as an individual prescreening modality [51, 64].

4.2.4 Germline Mutation Testing

This is the gold standard test to confirm the diagnosis of LS. A pathogenic germline mutation in the mismatch repair (MMR) or EPCAM gene is required for a definitive diagnosis of Lynch syndrome. Genome sequencing with different assays are done to identify MMR gene mutations. At times, even after the positive results from IHC or MSI testing, there are negative reports seen on the germline sequencing performed for the known MMR mutations [69–71]. This discrepancy can be due to the failure of the sequencing assays or due to somatic biallelic mutations in MSH2 or MLH1 [71, 72]. The patients with these discordant results are coined as with Lynch-like syndrome [69, 70].

Types of germline mutation testing:

1. Multigene panel testing—a multigene panel that includes *MLH1*, *MSH2*, *MSH6*, and *PMS2* as well as *EPCAM* deletion analysis and other genes of interest can be tested. This is the most often used method.
2. Serial single gene testing—When IHC staining shows loss of expression of one or more MMR genes, specific single-gene testing can be done. However, the correlation is not 100% and testing of more than one gene may be necessary, so, it is not cost-effective.
3. Comprehensive genomic testing—exome sequencing and genomic sequencing. This may be helpful when there is a discrepancy between the initial testing by IHC/MSI and the confirmatory germline mutation testing and provides a diagnosis for suspected Lynch-like syndrome cases.

The American Society of Clinical Oncology and The National Comprehensive Cancer Network recommend universal screening for Lynch syndrome in colorectal cancers [4, 73]. However, at present there is no guideline for universal screening of endometrial cancers for LS. The Society of Gynecologic Oncology and the American College of Obstetricians and Gynecologists do support both targeted and universal screening approach for LS in endometrial cancer patients. The Society of

Table 4.5 Lynch syndrome risk assessment: Society of Gynecologic Oncology guidelines [74]

1.	Evidence of microsatellite instability or loss of DNA mismatch repair protein (MLH1, MSH2, MSH6, PMS2) on immunohistochemistry in a patient with endometrial or colorectal cancer
2.	First-degree relative with endometrial or colorectal cancer who was either diagnosed before 60 years of age or who is identified as high risk by a systematic clinical screen which includes focused medical and personal medical history
3.	First- or second-degree relative with a known mutation in a mismatch repair gene

Gynecologic Oncology guidelines [51, 74, 75] recommend testing for Lynch syndrome (Table 4.5) in women with endometrial cancer with any of the following:

- Age at diagnosis less than 50 years
- Presence of LS-related tumors (synchronous or metachronous) irrespective of the age
- Histopathology showing infiltration of lymphocytes or peritumoral lymphocytes, or the undifferentiated type; origin at lower uterine segment at less than 60 years of age
- Family history of Lynch-associated tumor in one or more first-degree relatives with diagnosis at less than 50 years of age
- Diagnosis of endometrial or colorectal cancer in two or more first- or second-degree relatives with Lynch-associated tumors irrespective of age
- Presence of a known mismatch repair gene in a first- or second-degree relative

However, these screening guidelines may miss the diagnosis of LS in patients with EC because of the narrow screening criteria.

Due to the abovementioned limitations of targeted screening and single test screening models, several studies investigated a combination of laboratory methods for all newly diagnosed endometrial cancers. For example, in a study by Buchanan et al., when IHC staining was combined with MLH1 methylation, it resulted in increased positive predictive value to identify LS individuals in comparison to MSI testing by PCR [76]. Wang et al. [77] have provided an algorithm (Fig. 4.1) for a multistep approach for newly diagnosed endometrial cancers.

4.3 Cowden Syndrome

Cowden syndrome (CS) is a part of the PTEN hamartoma sequence and is a multiple hamartoma syndrome with a high risk for benign and malignant tumors of the thyroid, breast, endometrium, skin, brain, and gastrointestinal [78]. It is an autosomal dominant syndrome due to a mutation in the phosphatase and tensin homolog (PTEN) tumor suppressor gene. Apart from the malignant lesions, other features are the presence of macrocephaly, thyroid disease, hamartomatous GI tract polyps, and benign cystic breast disease. The cutaneous manifestations are mucocutaneous lesions (facial tricholemmomas, acral keratoses, papillomatous oral lesions),

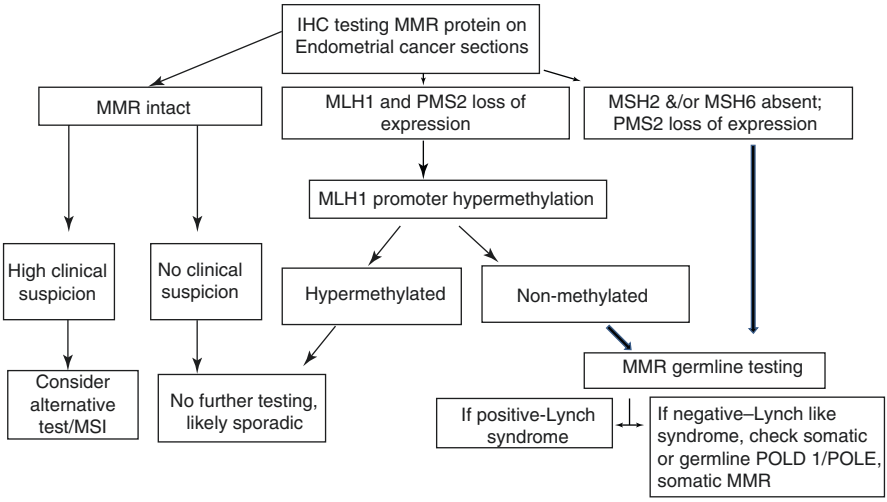


Fig. 4.1 Algorithm used for universal Lynch syndrome screening in newly diagnosed endometrial cancers using MMR IHC; methylation-specific polymerase chain reaction, (Adapted from Wang et al., 2018, reference—[77])

lipomas, and fibromas [79]. The reported cumulative lifetime risk of endometrial cancer in women with CS varies from 13 to 28% [78, 80–82].

Carriers of this gene variant have an increased risk of EC starting at the age of 25 years, but case reports have shown the cancer developing during adolescence as early as 14 years [83]. Endometrioid histology is reported to be the most prevalent type in individuals who carry a PTEN pathogenic variant [84].

Since EC forms the major diagnostic criterion for the diagnosis of CS, clinical testing of PTEN is thereby suggested when women with endometrial cancer have clinical features of CS or they give a family history of the same. Also, testing for PTEN pathogenic variant should be done when endometrial cancer presents at a younger age, especially adolescence. Currently, population-based testing is not recommended for CS due to its rare occurrence and is being performed only for research purposes.

4.4 POLD1 and POLE Mutations

The POLD1 gene encodes the catalytic and proofreading subunit of DNA polymerase δ and POLE gene encodes the catalytic subunit of DNA polymerase ε. DNA polymerases are involved in the DNA replication system. These are specifically required for the recognition and removal of mis-paired bases that occur during the replication process and act as proofreaders [85, 86].

The mutations in POLD1 and POLE genes are recently reported to cause multiple colonic adenomas and colorectal cancer, and mutation in POLD1 (p.Ser478Asn) predisposes to early-onset endometrial cancer and brain tumors [87]. These

mutations affect the exonuclease site of the DNA polymerase enzyme and thereby result in additional mutations in the DNA replication system. POLE gene mutations have been reported in sporadic endometrial cancers. The somatic mutations in POLE are seen in about 7% of EC, mostly in FIGO grade 3 endometrioid type and have 100% progression-free survival rate [13, 88].

At present, no POLD1 gene mutations have been reported in sporadic EC and there is no prognostic significance known for this mutation. However, POLD 1 germline mutation has been reported and might carry a risk of having secondary tumors in a hereditary syndromic way [9]. Both POLE and POLD1 mutations have been reported in colorectal cancers and have been defined as part of the *polymerase proofreading-associated polyposis syndrome* [89]. It is an autosomal dominant highly penetrant syndrome with oligo-adenomatous polyposis along with the development of CRC and EC at an early age. POLE mutations are more common in ECs patients while POLD1 is more frequently found in colorectal adenocarcinoma patients [87, 90]. Wong et al. [91] reported Pathogenic POLE (somatic or germline) and POLD1 germline mutations in 29.7% (14/47) and 4.3% (2/47) patients with FIGO grade 3 endometrioid cancer. Also, they highlighted that these tumors were *microsatellite stable,* with *peritumoral lymphocytic infiltration* and these can be used as distinguishing features of these mutations in grade 3 endometrioid cancers.

Currently, little is known about the POLE and POLD1 germline mutations and further studies are required to estimate the incidence of this hereditary cancer syndrome and risk of POLD 1germline mutations.

4.5 BRCA Mutations

BRCA mutation carriers have an increased risk of breast and ovarian cancer. Few studies state that BRCA1 carriers have an increased risk of endometrial cancer. A multinational cohort study by Thompson et al., involving 11,847 BRCA1 mutation carriers, reported an increase in the risk of cancer of uterine body (RR 2.65, 95% CI 1.69–4.16) [92].

A subsequent prospective study reported that the risk of EC in BRCA1 carriers is significantly higher only for the women who were on Tamoxifen [93]. Further studies are required to estimate the role of BRCA mutations in increasing EC risk. Few studies have reported an increased association of uterine serous papillary carcinoma with BRCA mutations [94–96]. Due to the conflicting results of different studies, it is not suggested to undergo routine population testing for BRCA mutations on patients of endometrial cancer, unless clinically warranted and for research purposes.

4.6 Genetic Polymorphisms

The genetic polymorphisms that involve a single base pair are termed as single nucleotide polymorphisms (SNPs, pronounced as snips). When these are located within a gene or in a regulatory region near a gene, they can be involved directly in

the causation of a disease by affecting the gene's function. Large-scale candidate locus analysis and genome-wide association analysis have shown that many common SNPs can be involved in increasing the risks of endometrial cancer. These are the 'low-risk' SNPs at/near HNF1B [97, 98], the TERT-CLPTM1L cancer risk region [99], the CYP19A1 locus encoding the aromatase enzyme pivotal to estrogen biosynthesis [100], ESR1 encoding the estrogen receptor [101], SH2B3 [102], SOX4 [103], KLF5, AKT1, EIF2AK4, HEY2/NCOA7, and at the MYC multicancer locus [104]. With these SNPs, there is a modest risk of endometrial cancer (odds ratios (OR)—0.84 to 1.27). Altogether, the abovementioned loci may account for approximately 5% of the familial endometrial cancers.

4.7 Endometrial Cancer Surveillance in Mutation Carriers

Once the diagnosis of endometrial cancer is made in a woman, she should be evaluated for the endometrial cancer predisposing syndromes. This includes a detailed family history, clinical examination in relation to the various cancer syndromes along with molecular studies (MSI testing and/or immunohistochemistry [IHC]) on the tumor. Once the patient is positive for the family history or the tumor studies come as positive for any of the pathological variants, she should be referred to a geneticist in a high-risk oncology unit [105].

The advantage of genetic testing is the prevention of further development of other cancers by screening and prophylactic measures. Also, it adds to the testing of the other family members for the specific mutations. This helps in providing screening and prophylactic measures to the individuals affected by the same or different mutations. Family members of the patient should be counselled regarding the cancer risks and should be provided the available screening measures.

Women who are carriers of Lynch mutations (Table 4.1) are advised yearly endometrial sampling, beginning at 30–35 years of age or 5–10 years earlier than the age at which the first diagnosis of the syndrome-related cancer in the family [80, 106].

Some experts have suggested the use of transvaginal ultrasonography (TVUS) for screening for endometrial cancer; however, it does not increase sensitivity when combined with endometrial sampling in comparison to sampling alone. Its main use has been seen in screening for ovarian cancer in these women. There is no sufficient data to differentiate between the endometrial sampling and TVUS as screening modalities for women with Lynch syndrome. For now, only endometrial sampling is considered the procedure of choice, though being invasive, it must be performed annually.

There are no well-defined recommendations for endometrial cancer surveillance for women with CS; annual endometrial sampling is suggested beginning at age 30–35, or 5 years younger than the earliest familial endometrial cancer diagnosis, for premenopausal women and annual transvaginal ultrasound examination for postmenopausal women can be considered.

Since the risk of endometrial cancer in BRCA mutation carriers is not well defined, at present there is no recommendation for screening them. However, screening has to be done for patients on Tamoxifen and those who give a family history of uterine cancer.

4.7.1 Chemoprevention

Though the use of OCPs and depo-provera has proven to decrease the proliferation of the endometrium in women with Lynch syndrome [40], they have not been recommended to be used as a preventive measure in these women.

4.7.2 Prophylactic Surgery

The women who are carriers of mutations in MMR gene are suggested to undergo prophylactic hysterectomy and bilateral salpingo-oophorectomy at the end of childbearing or around the age of 40 years.

Since these women are at high risk of colorectal, endometrial, and ovarian cancer, preoperative assessment must include an endometrial sampling, transvaginal ultrasound (TVUS), and cancer antigen 125 (CA 125) along with appropriate colorectal cancer screening.

Women who develop colorectal cancer as the sentinel cancer should be advised to undergo concurrent prophylactic hysterectomy and bilateral salpingo-oophorectomy.

The uterus, ovaries, and bowel should be carefully examined at the time of surgery as there are chances of the patient harboring an occult carcinoma [36, 107]. Frozen sections of the uterus and ovary can be sent if occult carcinoma is suspected and the performing surgical team must be prepared to perform a complete staging procedure.

No specific recommendation is provided for choosing a subtotal or a total hysterectomy, but, since the cervix is the usual mode of spread of endometrial cancer, it is advisable to perform a total hysterectomy.

Prophylactic hysterectomy should be considered in a similar way in Cowden syndrome. In BRCA mutation carriers, women who are on Tamoxifen can be offered preventive bilateral salpingo-oophorectomy.

Advantages of testing all newly diagnosed endometrial cancer are multiple. First of all, it differentiates between the sporadic and inherited endometrial cancers. This is important for genetic counselling of the patients affected for an effective follow-up of other associated cancers. It also helps in screening the family members of the patients for the specified mutation and thereby offering the chemoprevention and prophylactic risk-reducing surgeries. It can also prove helpful in the management of endometrial cancers that are resistant to the usual course of treatment.

4.8 Conclusions

Lynch syndrome and Cowden syndrome are considered the most common causes of hereditary endometrial cancer and at present, only six genes are thought to be relevant for testing the women with endometrial cancer, the MMR genes (MLH1, MSH2, MSH6, PMS2), EPCAM deletion, and PTEN. Recent studies mention POLD1 and POLE as important familial cancer genes; however, the absolute risks associated with endometrial cancer with these genes are not clear. Also, currently, there is no evidence to recommend testing for BRCA gene mutations without clinical suspicion. Universal screening for endometrial cancer in low-risk population is not recommended, but routine screening by endometrial sampling is recommended in women with inheritable germline mutations and they should be offered prophylactic hysterectomy.

Key Points

1. EC is the most common gynecological cancer in the developed world and is on the rise in the developing world.
2. Three to 5% of endometrial cancers are inherited.
3. At present, there is no recommendation of universal screening for Lynch syndrome on all newly diagnosed endometrial cancers; however, most societies support targeted and stepwise screening approach.
4. Women with EC who are suspected to have a germline mutation based on family history or tumor testing should be referred to a geneticist for genetic counselling.
5. These women come under the "high risk" category for endometrial cancer and routine screening is recommended by yearly endometrial sampling starting at the age of 30–35 years.
6. Prophylactic hysterectomy with/without bilateral salpingo-oophorectomy (depending upon the germline mutation involved) is suggested at the end of childbearing or 40 years.

References

1. Bray F, Ferlay J, Soerjomataram I, et al. GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018. In press
2. http://seer.cancer.gov/statfacts/html/corp.html. (2013–2015 data).
3. Win AK, Reece JC, Ryan S. Family history and risk of endometrial cancer: a systematic review and meta-analysis. Obstet Gynecol. 2015;125:89–98.
4. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223–62.
5. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology clinical practice guidelines. J Clin Oncol. 2015;33:209–17.

6. Ngeow J, Eng C. PTEN hamartoma tumor syndrome: clinical risk assessment and management protocol. Methods. 2015;77-78:11–9.
7. Ngeow J, Sesock K, Eng C. Breast cancer risk and clinical implications for germline PTEN mutation carriers. Breast Cancer Res Treat. 2015;165:1–8. https://doi.org/10.1007/s10549-015-3665-z.
8. Petrucelli N, Daly MB, Feldman GL. BRCA1 and BRCA2 hereditary breast and ovarian cancer. In: Pagon RA, Adam MP, Ardinger HH, et al., editors. Gene reviews (R): University of Washington. WA, USA: Seattle; 2013.
9. Bellido F, Pineda M, Aiza G, et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. Genet Med. 2015;18(4):325–32.
10. Daniels MS. Genetic testing by cancer site: uterus. Cancer J. 2012;18(4):338–42.
11. Peltomaki P. Update on Lynch syndrome genomics. Familial Cancer. 2016;15:385–93.
12. Meyer LA, Broaddus RR, Lu KH, et al. Endometrial cancer and Lynch syndrome: clinical and pathologic considerations. Cancer Control. 2009;16:14–22.
13. Kandoth C, Schultz N, Cherniack AD, et al. Cancer genome atlas research. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497:67–73.
14. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA. 2011;305:2304–10.
15. Moller P, Seppala T, Bernstein I, et al. Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the prospective Lynch syndrome database. Gut. 2017;66:464.
16. Baglietto L, Lindor NM, Dowty JG, et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. J Natl Cancer Inst. 2010;102:193.
17. Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology. 2008;135:419.
18. Hampel H, de la Chapelle A. How do we approach the goal of identifying everybody with Lynch syndrome? Familial Cancer. 2013;12:313–7.
19. Vynogradova RP, Babenko OIu, Klymenko OF, et al. Cyclic nucleotides in a high molecular weight aminoacyl-tRNA synthetase complex from the liver of normal and irradiated rats. Ukr Biokhim Zh (1978) 1990; 62:100.
20. Vasen HF, Watson P, Mecklin JP, Lynch HT. New criteria for hereditary nonpolyposis colorectal cancer(HNPCC) proposed by the international collaborative group on HNPCC. Gastroenterology. 1999;116(6):1453–6.
21. Lynch HT, Shaw MW, Magnuson CW, et al. Hereditary factors in cancer. Study of two large midwestern kindreds. Arch Intern Med. 1966;117:206–12.
22. Committee opinion no. 634. Hereditary cancer syndromes and risk assessment. Obstet Gynecol. 2015;125:1538.
23. Lu KH, Dinh M, Kohlmann W, et al. Gynaecologic cancer as a "sentinel cancer" for women with hereditary nonpolyposis colorectal cancer syndrome. Obstet Gynecol. 2005;105:569–74.
24. Kempers MJ, Kuiper RP, Ockeloen CW, et al. Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. Lancet Oncol. 2011;12:49–55.
25. Jass JR, Cottier DS, Jeevaratnam P, et al. Diagnostic use of microsatellite instability in hereditary non-polyposis colorectal cancer. Lancet. 1995;346:1200–1.
26. Parsons R, Li GM, Longley MJ, et al. Hypermutability and mismatch repair deficiency in RER tumor cells. Cell. 1993;75:1227–36.
27. Umar A, Boyer JC, Thomas DC, et al. Defective mismatch repair in extracts of colorectal and endometrial cancer cell lines exhibiting microsatellite instability. J Biol Chem. 1994;269:14367–70.
28. Goodfellow PJ, Buttin BM, Herzog TJ, et al. Prevalence of defective DNA mismatch repair and MSH6 mutation in an unselected series of endometrial cancers. Proc Natl Acad Sci U S A. 2003;100:5908.

29. Stefansson I, Akslen LA, MacDonald N, et al. Loss of hMSH2 and hMSH6 expression is frequent in sporadic endometrial carcinomas with microsatellite instability: a population-based study. Clin Cancer Res. 2002;8:138.
30. Chadwick RB, Pyatt RE, Niemann TH, et al. Hereditary and somatic DNA mismatch repair gene mutations in sporadic endometrial carcinoma. J Med Genet. 2001;38:461.
31. Black D, Soslow RA, Levine DA, et al. Clinicopathologic significance of defective DNA mismatch repair in endometrial carcinoma. J Clin Oncol. 2006;24:1745.
32. Peltomaki P. Role of DNA mismatch repair defects in the pathogenesis of human cancer. J Clin Oncol. 2003;21:1174–9.
33. Dunlop MG, Farrington SM, Nicholl I, et al. Population carrier frequency of hMSH2 and hMLH1 mutations. Br J Cancer. 2000;83:1643.
34. Vasen HF, Stormorken A, Menko FH, et al. MSH2 mutation carriers are at higher risk of cancer than MLH1 mutation carriers: a study of hereditary nonpolyposis colorectal cancer families. J Clin Oncol. 2001;19:4074.
35. Boks DE, Trujillo AP, Voogd AC, et al. Survival analysis of endometrial carcinoma associated with hereditary nonpolyposis colorectal cancer. Int J Cancer. 2002;102:198.
36. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med. 2006;354:261.
37. Hampel H, Frankel W, Panescu J, et al. Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res. 2006;66:7810.
38. Balmana J, Stockwell DH, Steyerberg EW, et al. Prediction of MLH1 and MSH2 mutations in Lynch syndrome. JAMA. 2006;296:1469–78.
39. Dashti SG, Chau R, Ouakrim DA, et al. Female hormonal factors and the risk of endometrial cancer in Lynch syndrome. JAMA. 2015;314:61.
40. Lu KH, Loose DS, Yates MS, et al. Prospective multicentre randomized intermediate biomarker study of oral contraceptive versus Depo-Provera for prevention of endometrial cancer in women with Lynch syndrome. Cancer Prev Res (Phila). 2013;6(8):774–81.
41. Obermair A, Youlden DR, Young JP, et al. Risk of endometrial cancer for women diagnosed with HNPCC-related colorectal carcinoma. Int J Cancer. 2010;127:2678–84.
42. Watson P, Bützow R, Lynch HT, et al. The clinical features of ovarian cancer in hereditary nonpolyposis colorectal cancer. Gynecol Oncol. 2001;82:223–8.
43. Buchanan DD, Tan YY, Walsh MD, et al. Tumor mismatch repair immunohistochemistry and DNA MLH1 methylation testing of patients with endometrial cancer diagnosed at age younger than 60 years optimizes triage for population-level germline mismatch repair gene mutation testing. J Clin Oncol. 2014;32:90–100.
44. Garg K, Leitao MM Jr, Kauff ND, et al. Selection of endometrial carcinomas for DNA mismatch repair protein immunohistochemistry using patient age and tumor morphology enhances detection of mismatch repair abnormalities. Am J Surg Pathol. 2009;33:925.
45. 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;26:5965–71.
46. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med. 2009;11(1):42–65.
47. Goodenberger M, Lindor NM. Lynch syndrome and MYH associated polyposis: review and testing strategy. J Clin Gastroenterol. 2011;45(488–500):38.
48. Rodriguez-Bigas MA, Boland CR, Hamilton SR, et al. A National Cancer Institute workshop on hereditary nonpolyposis colorectal cancer syndrome: meeting highlights and Bethesda guidelines. J Natl Cancer Inst. 1997;89:1758–62.
49. Lin DI, Hecht JL. Targeted screening with combined age- and morphology-based criteria enriches detection of Lynch syndrome in endometrial cancer. Int J Surg Pathol. 2016;24:297–305.
50. Garg K, Soslow RA. Lynch syndrome (hereditary non-polyposis colorectal cancer) and endometrial carcinoma. J Clin Pathol. 2009;62:679–84.

51. American College of Obstetricians and Gynecologists. Lynch syndrome. Practice bulletin no. 147. Obstet Gynecol. 2014;124:1042–54.
52. Goodfellow PJ, Billingsley CC, Lankes HA, et al. Combined microsatellite instability, MLH1 methylation analysis, and immunohistochemistry for Lynch syndrome screening in endometrial cancers from GOG210: an NRG oncology and gynecologic oncology group study. J Clin Oncol. 2015;33(36):4301–8.
53. Mills AM, Liou S, Ford JM, Berek JS, Pai RK, Longacre TA. Lynch syndrome screening should be considered for all patients with newly diagnosed endometrial cancer. Am J Surg Pathol. 2014;38(11):1501–9.
54. Resnick KE, Hampel H, Fishel R, Cohn DE. Current and emerging trends in Lynch syndrome identification in women with endometrial cancer. Gynecol Oncol. 2009;114:128–34.
55. Barnetson RA, Tenesa A, Farrington SM, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med. 2006;354:2751.
56. Wijnen JT, Vasen HF, Khan PM, et al. Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. N Engl J Med. 1998;339:511.
57. Kastrinos F, Ojha RP, Leenen C, et al. Comparison of prediction models for Lynch syndrome among individuals with colorectal cancer. J Natl Cancer Inst. 2016;108
58. Chen S, Wang W, Lee S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA. 2006;296:1479–87.
59. Balaguer F, Balmaña J, Castellví-Bel S, et al. Validation and extension of the PREMM1, 2 model in a population-based cohort of colorectal cancer patients. Gastroenterology. 2008;134:39–46.
60. Niu B, Ye K, Zhang Q, et al. MSIsensor: microsatellite instability detection using paired tumor normal sequence data. Bioinformatics. 2014;30:1015.
61. Huang MN, McPherson JR, Cutcutache I, et al. MSIseq: software for assessing microsatellite instability from catalogs of somatic mutations. Sci Rep. 2015;5:13321.
62. Berg AO, Grp EW, Armstrong K, et al. Recommendations from the EGAPP working group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med. 2009;11:35–41.
63. Mills AM, Sloan EA, Thomas M, et al. Clinicopathologic comparison of Lynch syndrome-associated and "Lynch-like" endometrial carcinomas identified on universal screening using mismatch repair protein immunohistochemistry. Am J Surg Pathol. 2016;40:155–65.
64. Mills AM, Longacre TA. Lynch syndrome screening in the gynecologic tract: current state of the art. Am J Surg Pathol. 2016;40:e35–44.
65. 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;137(2):306–10.
66. Moline J, Mahdi H. B. Yang, et al. implementation of tumor testing for Lynch syndrome in endometrial cancers at a large academic medical Centre. Gynecol Oncol. 2013;130:121–6.
67. Heald B, Plesec T, Liu X, et al. Implementation of universal microsatellite instability and immunohistochemistry screening for diagnosing Lynch syndrome in a large academic medical center. J Clin Oncol. 2013;31:1336–40.
68. Bruegl AS, Ring KL, Daniels M, et al. Clinical challenges associated with universal screening for Lynch syndrome–associated endometrial cancer. Cancer Prev Res (Phila). 2017;10:108–15.
69. Rodríguez-Soler M, Pérez-Carbonell L, Guarinos C, et al. Risk of cancer in cases of suspected Lynch syndrome without germline mutation. Gastroenterology. 2013;144:926–32.
70. Mas-Moya J, Dudley B, Brand RE, et al. Clinicopathological comparison of colorectal and endometrial carcinomas in patients with Lynch-like syndrome versus patients with Lynch syndrome. Hum Pathol. 2015;46:1616–25.
71. Carethers JM. Differentiating Lynch-like from Lynch syndrome. Gastroenterology. 2014 Mar;146:602–4.

72. Mensenkamp AR, Vogelaar IP, Van Zelst-Stams WA, et al. Somatic mutations in MLH1 and MSH2 are a frequent cause of mismatch-repair deficiency in Lynch syndrome–like tumors. Gastroenterology. 2014;146:643–6.
73. Lu KH, Ring KL. One size may not fit all: the debate of universal tumor testing for Lynch syndrome. Gynecol Oncol. 2015;137:2–3.
74. Lancaster JM, Powell CB, Chen LM, et al. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. Gynecol Oncol. 2015;136:3–7.
75. Randall LM, Pothuri B, Swisher EM, et al. Multi-disciplinary summit on genetics services for women with gynecologic cancers: a Society of Gynecologic Oncology White Paper. Gynecol Oncol. 2017;146:217.
76. Buchanan DD, Clendenning M, Rosty C, et al. Tumor testing to identify Lynch syndrome in two Australian colorectal cancer cohorts. J Gastroenterol Hepatol. 2017;32(2):427–38.
77. Wang A, McCracken J, Li Y, Xu L. The practice of universal screening for Lynch syndrome in newly diagnosed endometrial carcinoma. Health Sci Rep. 2018 Jul;1(7):e43.
78. Tan MH, Mester JL, Ngeow J, et al. Lifetime cancer risks in individuals with germline PTEN mutations. Clin Cancer Res. 2012;18:400–7.
79. Starink TM, Hausman R. The cutaneous pathology of extrafacial lesions in Cowden's disease. J Cutan Pathol. 1984;11:338–44.
80. Pilarski R, Stephens JA, Noss R, et al. Predicting PTEN mutations: an evaluation of Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome clinical features. J Med Genet. 2011;48:505.
81. Heald B, Mester J, Rybicki L, et al. Frequent gastrointestinal polyps and colorectal adenocarcinomas in a prospective series of PTEN mutation carriers. Gastroenterology. 2010;139:1927.
82. Riegert-Johnson DL, Gleeson FC, Roberts M, et al. Cancer and Lhermitte-Duclos disease are common in Cowden syndrome patients. Hered Cancer Clin Pract. 2010;8:6.
83. Baker WD, Soisson AP, Dodson MK. Endometrial cancer in a 14-year-old girl with Cowden syndrome: a case report. J Obstet Gynaecol Res. 2013;39:876.
84. Mahdi H, Mester JL, Nizialek EA, et al. Germline PTEN, SDHB-D, and KLLN alterations in endometrial cancer patients with Cowden and Cowden-like syndromes: an international, multicenter, prospective study. Cancer. 2015;121:688–96.
85. Burgers PM. Polymerase dynamics at the eukaryotic DNA replication fork. J Biol Chem. 2009;284(4041–4045):52.
86. Hindges R, Hubscher U. DNA polymerase delta, an essential enzyme for DNA transactions. Biol Chem. 1997;378:345–62.
87. Palles C, Cazier JB, Howarth KM, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet. 2013;45:136–44.
88. 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;134:15–9.
89. Church JM. Polymerase proofreading-associated polyposis: a new, dominantly inherited syndrome of hereditary colorectal cancer predisposition. Dis Colon Rectum. 2014;57:396–7.
90. Church DN, Briggs SE, Palles C, et al. DNA polymerase epsilon and delta exonuclease domain mutations in endometrial cancer. Hum Mol Genet. 2013;22:2820–8.
91. Wong A, Kuick CH, Wong WL, et al. Mutation spectrum of POLE and POLD1 mutation. South east Asian women presenting with grade 3 endometrioid endometrial carcinoma. Gynecol Oncol. 2016 Apr;141(1):113–20.
92. Thompson D, Easton DF. Breast cancer linkage consortium. Cancer incidence in BRCA1 mutation carriers. J Natl Cancer Inst. 2002;94:1358.
93. Beiner ME, Finch A, Rosen B, et al. The risk of endometrial cancer in women with BRCA1 and BRCA2 mutations. A prospective study. Gynecol Oncol. 2007;104:7.
94. Biron-Shental T, Drucker L, Altaras M, et al. High incidence of BRCA1-2 germline mutations, previous breast cancer and familial cancer history in Jewish patients with uterine serous papillary carcinoma. Eur J Surg Oncol. 2006;32:1097.

95. Hornreich G, Beller U, Lavie O, et al. Is uterine serous papillary carcinoma a BRCA1-related disease? Case report and review of the literature. Gynecol Oncol. 1999;75:300.
96. Lavie O, Hornreich G, Ben Arie A, et al. BRCA1 germline mutations in women with uterine serous papillary carcinoma. Obstet Gynecol. 2000;96:28.
97. Spurdle AB, Thompson DJ, Ahmed S, et al. Genomewide association study identifies a common variant associated with risk of endometrial cancer. Nat Genet. 2011;43:451–4.
98. Painter JN, O'Mara TA, Batra J, et al. Fine-mapping of the HNF1B multicancer locus identifies candidate variants that mediate endometrial cancer risk. Hum Mol Genet. 2015;24:1478–92.
99. Carvajal-Carmona LG, O'Mara TA, Painter JN, et al. Candidate locus analysis of the TERT-CLPTM1L cancer risk region on chromosome 5p15 identifies multiple independent variants associated with endometrial cancer risk. Hum Genet. 2015;134:231–45.
100. Setiawan VW, Doherty JA, Shu XO, et al. Two estrogen-related variants in CYP19A1 and endometrial cancer risk: a pooled analysis in the epidemiology of endometrial cancer consortium. Cancer Epidemiol Biomark Prev. 2009;18:242–7.
101. O'Mara TA, Glubb DM, Painter JN, et al. Comprehensive genetic assessment of the ESR1 locus identifies a risk region for endometrial cancer. Endocr Relat Cancer. 2015;22:851–61.
102. Cheng TH, Thompson D, Painter J, et al. Meta-analysis of genome-wide association studies identifies common susceptibility polymorphisms for colorectal and endometrial cancer near SH2B3 and TSHZ1. Sci Rep. 2015;5:17369.
103. Chen MM, O'Mara TA, Thompson DJ, et al. GWAS meta-analysis of 16 852 women identifies new susceptibility locus for endometrial cancer. Hum Mol Genet. 2016;25:2612–20.
104. Cheng TH, Thompson DJ, O'Mara TA, et al. Five endometrial cancer risk loci identified through genome-wide association analysis. Nat Genet. 2016;48:667–74.
105. Kwon JS, Scott JL, Gilks CB, et al. Testing women with endometrial cancer to detect Lynch syndrome. J Clin Oncol. 2011;29:2247.
106. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US multi-society task force on colorectal cancer. Dis Colon Rectum. 2014;57:1025.
107. Pistorius S, Kruger S, Hohl R, et al. Occult endometrial cancer and decision making for prophylactic hysterectomy in hereditary nonpolyposis colorectal cancer patients. Gynecol Oncol. 2006;102:189.

Part II

Update in Treatment of Endometrial Cancer

Lymphadenectomy in Endometrial Cancer: Present Status

5

Neha Kumar

5.1 Introduction

The standard management of early-stage endometrial cancer includes surgical staging which comprises of total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment. Surgical staging helps determine the FIGO stage of the disease, as well as assess the pathological data and risk factors which help guide adjuvant treatment, if any. Prognostic factors include tumor size, grade of the lesion, depth of myometrial invasion, lymphovascular space invasion (LVSI), lymph node status, and tumor involvement of the lower uterine segment. Lymph node evaluation in surgical staging consists of bilateral pelvic nodal dissection with or without para-aortic lymph node dissection. The template for pelvic lymph node dissection is common iliac bifurcation cephalad, deep circumflex iliac vein caudad, internal iliac artery medially, genitofemoral nerve laterally, and obturator nerve at the base. The template for para-aortic node dissection is renal vessels cephalad, common iliac bifurcation caudad, and bilateral ureters on each side (Fig. 5.1). Para-aortic lymph node dissection is done in addition to pelvic nodal dissection in high-risk tumors such as high-grade endometrioid histology with >50% myometrial invasion, uterine papillary serous carcinoma, clear cell carcinoma, and carcinosarcoma. However, lymph node dissection is associated with intraoperative complications like blood vessel injury, increased blood loss, and nerve injury (obturator nerve and genitofemoral nerve) and postoperative complications like ileus, lymphocyst, and lymphedema. The incidence of lymphedema is reported between 1.2 and 47%, depending on the assessment method, and increases with postoperative radiotherapy [1].

Therapeutic role of lymphadenectomy is debatable, especially in patients with negative staging. Although the data is limited by retrospective studies, proponents of lymphadenectomy emphasize that complete lymphadenectomy helps accurately stage the disease and direct adjuvant therapy, provides prognostic information and

N. Kumar (✉)
Gynecologic Oncology, BLK Superspeciality Hospital, New Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_5

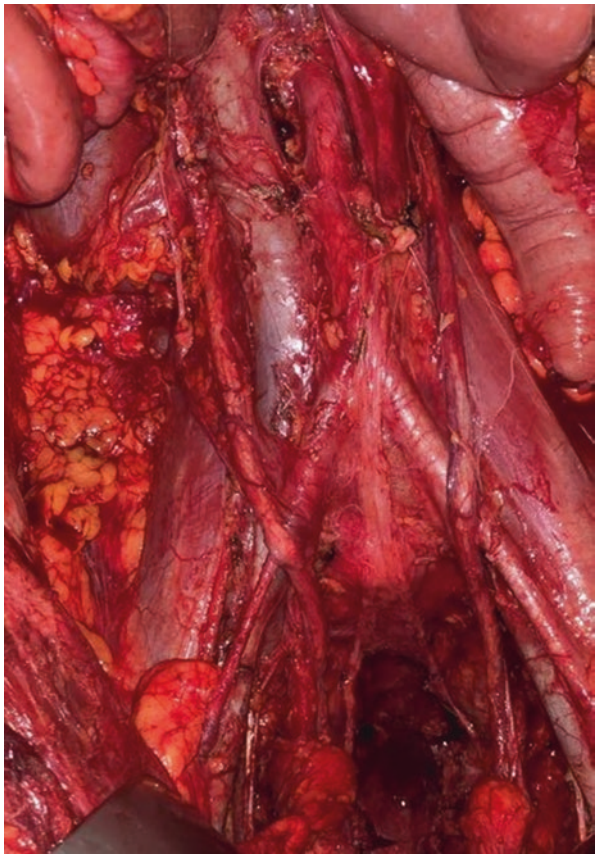


Fig. 5.1 Complete pelvic and para-aortic node dissection

also gives therapeutic benefit by removing metastatic disease in the involved nodes. Criticisms of lymphadenectomy, besides its associated morbidity, include lack of randomized trials that show a therapeutic benefit of lymphadenectomy. In fact, the published randomized trials comparing lymphadenectomy versus no lymphadenectomy in endometrial cancer have not shown any survival benefit with lymphadenectomy in low-risk patients.

Selective use of lymphadenectomy is recommended in early-stage endometrial cancer as it can reduce the morbidity associated with lymph node dissection without compromising clinical outcomes. Previously, a full lymphadenectomy, including both pelvic and para-aortic nodes was recommended for all patients irrespective of their risk factors. The recent NCCN (National Comprehensive Cancer Network) recommendations, however, favor selective lymphadenectomy including sentinel lymph node biopsy, to avoid overtreatment in low-risk patients [2]. Preoperative and intraoperative assessment of risk factors help decide whether to perform lymphadenectomy or not, and to what extent—pelvic nodes only or both pelvic and para-aortic nodes. Sentinel lymph node (SLN) mapping is an alternative to complete lymphadenectomy in the patients with disease confined to the uterus and no

evidence of metastasis on preoperative imaging studies or during intraoperative exploration. Close adherence to SLN surgical algorithm recommended by the NCCN, which includes a side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes is associated with a false-negative rate of less than 5% [3, 4]. Moreover, SLN mapping with ultrastaging often increases the detection of lymph node metastasis in comparison to routine lymphadenectomy due to removal of sentinel lymph nodes which may lie outside the standard template in a few cases, and extensive sectioning and evaluation of all sentinel lymph nodes.

5.2 Lymphadenectomy: All, None, or Selective

The uterus drains into the pelvic (iliac and obturator chains) and the para-aortic lymph nodes. Few lymphatic channels from the uterine fundus can drain directly into the para-aortic lymph node chain via the infundibulopelvic ligament. Tumors more than 2 cm in size, high-grade histologies, deep myometrial invasion, lymphovascular space invasion, cervical stromal involvement, and lower uterine segment involvement are associated with increased risk of lymph node metastasis. The risk of lymph node metastasis in non-endometrioid cancers (papillary serous, clear cell, carcinosarcoma) is as high as 40% compared with 16% with endometrioid histology [5]. The risk of metastasis in para-aortic lymph nodes with involved pelvic lymph nodes is approximately 50% [6]. The risk of isolated para-aortic metastasis (without pelvic lymph node involvement) is small—only 2–3%, but a few series have reported higher rates (16–45%) [5, 7, 8]. There has been much debate regarding lymphadenectomy in endometrial cancer—whether it should be routinely done in all patients, or avoided in low-risk early-stage patients, and used judiciously in patients with high risk of lymph node metastasis. Controversies have also existed about the extent of lymphadenectomy—both pelvic and para-aortic or only pelvic, and also the extent of para-aortic node dissection—up to inferior mesenteric artery or renal vessels.

5.2.1 Lymphadenectomy: All

Lymphadenectomy helps assess the nodal status and determine the stage of endometrial cancer accurately. Low-risk patients may avoid radiation after complete staging with lymphadenectomy, or may only receive vaginal brachytherapy. Without lymphadenectomy, the oncologist has to rely only on uterine risk factors to decide adjuvant treatment and hence many patients without lymph node assessment receive pelvic radiation. The studies that support routine lymphadenectomy in all the patients cite the inaccuracy of preoperative imaging, intraoperative assessment, and frozen section in predicting the risk for nodal disease. Only 10% of patients with lymph node metastasis have clinically enlarged nodes and even these can be missed by intraoperative palpation through the overlying peritoneum [7]. Inaccuracies in

determining grade of the lesion and depth of myometrial invasion with frozen section have been reported in up to 30% of cases [9]. Another advantage of routine lymphadenectomy is that it might provide a therapeutic benefit by removing any possible cancer in the lymph nodes and reducing the disease burden.

Retrospective studies have shown a benefit in removing bulky or involved lymph nodes during surgical staging. Havrilesky et al. noted that the 5-year disease-specific survival (DSS) was 63% in patients with lymph nodes showing microscopic disease, 50% in completely resected grossly positive nodes, and 43% in cases where bulky nodes could not be resected [10]. Bristow et al. reported that the median DSS in patients with completely debulked involved lymph nodes was 37.7 months, compared with 8.8 months in patients with gross residual lymph node disease [11]. Hence, there is definitely a survival benefit with debulking bulky involved lymph nodes and every effort must be made to completely resect all obvious lymph node metastases.

The therapeutic benefit of removing non-enlarged, negative lymph nodes has been controversial. Kilgore et al. retrospectively reviewed 649 women with stage I or II endometrial cancer—a third underwent complete lymphadenectomy, one-third had selective sampling, and the remaining third had no nodal sampling. Women who underwent multiple site pelvic nodal dissection (at least four pelvic nodal sites) and had a mean of 11 nodes removed, had improved survival compared with women who did not have any lymph nodes sampling. This advantage persisted even after stratification of cases into low and high risk, and irrespective of whether adjuvant radiation was used or not [12]. It is possible that improved outcomes in these cases were due to removal of lymph node micrometastases that could not be recognized by standard pathologic processing. Another study showing therapeutic benefit of lymphadenectomy was reported by Cragan et al., who demonstrated that removal of more than 11 pelvic lymph nodes was associated with improved overall and progression-free survival in patients with grade 3 endometrial cancers. The 5-year survival in patients with high-risk features like grade 3 lesions, >50% myometrial invasion, and serous or clear-cell histology was 82% when more than 11 nodes were removed compared to 64% when ≤11 nodes were removed. This benefit remained significant even after excluding patients who received adjuvant treatment [13].

The SEPAL study (Survival Effect of Para-Aortic Lymphadenectomy in endometrial cancer) from Japan evaluated the effect of para-aortic lymphadenectomy on survival in more than 600 patients. In intermediate and high-risk endometrial cancers, the recurrence-free survival and overall survival was significantly better in women who underwent combined pelvic and para-aortic lymphadenectomy than in those who had only pelvic lymphadenectomy. The survival benefit, however, did not extend to low-risk cancers [14]. The Mayo group found that when para-aortic nodes were positive, 77% of cases had positive nodes above the inferior mesenteric artery [5]. Hence, para-aortic node dissection is recommended till the level of renal vessels. Chan et al. reported the impact of complete lymphadenectomy on survival outcomes in over 12,000 women with endometrial cancer using the National Cancer Institute's SEER (Surveillance, Epidemiology, and End Results) data source. In patients with high-risk disease (IB grade 3, IC - FIGO 1988 Staging, II - IV), 5-year

survival was directly proportional to the number of nodes removed, increasing from 75% to 87% when 1 versus >20 nodes were removed [15].

The concept of lymph node (LN) ratio has been defined as the number of metastatic LNs to the total number of removed LNs. This ratio shows both the burden of nodal disease as well as the extent and quality of surgical staging. Patients with LN ratios of 10%, >10–50%, and >50% have reported to have overall survival rates of 79%, 61%, and 36%, respectively ($P < 0.001$) [16].

5.2.2 Lymphadenectomy: None

There are two prospective, randomized trials that have compared survival outcomes in women undergoing hysterectomy with or without lymphadenectomy in stage I–IIA endometrial cancer—the ASTEC (A Study in the Treatment of Endometrial Cancer) trial by Kitchener et al. [17] and the Italian trial by Benedetti et al. [18]. The ASTEC trial involved 1369 patients, who were further randomized to postoperative radiation or observation following surgery. Nodal status did not direct the use of adjuvant radiation therapy, and so even node-positive patients were randomized to the observation group. Moreover, vaginal brachytherapy could be given in both observation and radiation group depending upon the institutional preference. In the Italian trial (514 patients), postoperative radiation was not prescribed according to a set protocol but left to the oncologist's discretion. Both studies found no difference in survival outcomes between the two arms, and increased morbidity in the lymphadenectomy group. The authors concluded that there was no benefit in either progression-free or overall survival with lymphadenectomy and hence it could not be recommended as a routine procedure for therapeutic purposes.

These studies, however, have been criticized and their results should be interpreted with caution. There was overrepresentation of low-risk patients, especially in the ASTEC trial which could negate the beneficial effect of lymphadenectomy, if any, due to low incidence of lymph node metastasis in stage I low-risk disease. The quality of lymph node dissection in these trials has been questioned. Both trials were designed to evaluate only pelvic lymphadenectomy. Para-aortic lymphadenectomy was performed only in the Italian study and that too in only 26% of cases. In the ASTEC trial, 8% of patients in the lymphadenectomy group had no lymph node dissection and 12% of patients had less than five lymph nodes removed. There was a lack of standardization of adjuvant therapy such that only half of the patients with pelvic node metastases in the ASTEC study received pelvic radiation, thus limiting the benefit of identification of positive nodes. In the Italian trial, postoperative radiation or chemotherapy was given by the surgeon's preference. Other concerns include the lack of central pathology review, limited statistical power to show improvement in survival rates, and the lack of quality-of-life assessment. Despite these weaknesses, these two trials provide the only level 1 evidence on the role of lymphadenectomy in endometrial cancer. They show that lymphadenectomy may provide only modest survival benefit in early-stage disease and that removing negative nodes is unlikely to have any therapeutic role or improve survival outcomes.

The Cochrane 2017 review including 1851 patients reported no differences in overall and recurrence-free survival between women who underwent lymphadenectomy and those who did not undergo lymphadenectomy during surgical staging of endometrial cancer (pooled hazard ratio (HR) 1.07, 95% confidence interval (CI) 0.81 to 1.43 for overall survival; HR 1.23, 95% CI 0.96 to 1.58 for recurrence-free survival) [19]. There has been no evidence from any randomized trial that has shown the effect of lymphadenectomy in women with higher-stage disease and in cases at high risk of recurrence.

5.2.3 Lymphadenectomy: Selective

There are definite improved survival outcomes with debulking clinically enlarged, involved nodes or nodal macrometastasis, and possibly with resection of microscopic metastasis with pelvic and para-aortic lymphadenectomy in high-risk endometrial cancers. The therapeutic benefit of lymphadenectomy in node-negative patients is debatable.

The use of complete pelvic and para-aortic lymphadenectomy in all patients of endometrial cancer, irrespective of their risk factors, would result in overtreatment of a large fraction of low-risk patients who may not benefit from it, in addition to the surgical morbidity associated with systematic lymph node dissection. Various studies have focused on evaluating the patients' risk factors for lymph node metastasis as well as the status of lymph nodes. These factors, determined either preoperatively or intraoperatively, help decide which patients would benefit from lymphadenectomy and hence help tailor the lymph node dissection (pelvic, both pelvic and para-aortic or none) according to the risk factors in each patient.

Data from GOG 33 showed the rates of pelvic and para-aortic nodal disease with different grades and depth of myometrial invasion in endometrial cancers [7]. These could help decide whether or not to perform lymphadenectomy in patients, depending upon the risk of lymph node metastasis. The risk of pelvic nodal disease in GOG 33 was none for patients with grade 1 tumors with superficial invasion, but 11% for grade 1 tumors with deep myometrial invasion. Patients with grade 3 tumors and deep myometrial invasion were found to have pelvic nodal metastases in 34% and para-aortic nodal metastases in 23% cases (Table 5.1). Patients with serous or clear cell histology have nodal involvement in about 30–50% cases and warrant systematic pelvic and para-aortic lymphadenectomy even in the absence of myometrial invasion.

Mariani et al. described the Mayo's criteria in 2000, which helped identify a low-risk group of endometrial cancer that had a very small risk of nodal disease spread [5]. The criteria described were based on intraoperative frozen section of the uterine specimen—grade 1 to 2 endometrioid histology, less than 50% myometrial invasion, and tumor size less than 2 cm. In the study population of 422 patients, 27% (n = 122) were identified as low risk using the above parameters and none of these cases had lymph node metastasis. The negative predictive value of the Mayo's criteria in identifying a low-risk subset that would not benefit from lymphadenectomy

Table 5.1 Rates of pelvic and para-aortic lymph node metastases in different grades and depths of myometrial invasion in Endometrial Cancer [7]

Depth of myometrial invasion	Grade 1		Grade 2		Grade 3	
	Pelvic LN	Para-aortic LN	Pelvic LN	Para-aortic LN	Pelvic LN	Para-aortic LN
Confined to the endometrium	0%	0%	3%	3%	0%	0%
Inner third invasion	3%	1%	5%	4%	9%	4%
Middle third invasion	0%	5%	9%	0%	4%	0%
Outer third invasion	11%	6%	19%	14%	34%	23%

was 98%. The Mayo group uses these criteria for selective use of lymphadenectomy in management of patients with endometrial cancer. Their management protocol includes an intraoperative assessment of the hysterectomy specimen with frozen section. Women defined as low risk as per the Mayo's criteria do not undergo lymphadenectomy. Patients showing more than 50% myometrial invasion or Type II histology undergo both pelvic and aortic lymphadenectomy. Tumors not showing these features but having cervical invasion, grade 3 endometrioid histology with any myometrial invasion, or size larger than 2 cm, undergo pelvic lymphadenectomy. The pelvic lymph nodes are checked for metastasis by frozen section evaluation and para-aortic lymph node dissection is carried out if pelvic nodes are positive for disease [20].

The drawback of the Mayo criteria is that since it is based on intraoperative frozen section, it may not be replicated at many institutions with similar degree of accuracy. In fact, several institutions have reported upstaging in almost 18% cases on the final histopathological reports [9]. Due to these limitations, the Mayo group has now modified the criteria, the newer criteria using the grade of preoperative endometrial biopsy and intraoperative assessment of tumor size by the surgeon to determine whether to do lymphadenectomy or not [21]. Patients with grade 1 or 2 lesions on preoperative endometrial biopsy and tumor size less than 2 cm on intraoperative assessment by the surgeon, have less than 1% risk of lymph node metastasis and do not require lymphadenectomy. The surgeon should take care to avoid distorting the anatomy when opening the uterine specimen. Studies have reported that the visual inspection of more than or less than 50% myometrial invasion corresponds to the microscopic findings in 85% cases, although this accuracy decreases in grade 3 tumors [22, 23].

The European Society for Medical Oncology (ESMO) has categorized endometrial cancer into three risk groups—Low risk (Stage IA, grade 1 or 2), Intermediate risk (Stage IA, grade 3 and Stage IB, grade 1 or 2), and High risk (Stage IB, grade 3 and Type 2 histology). Due to the low risk of lymph node metastasis, ESMO does not recommend lymphadenectomy in the low-risk group [24].

Preoperative imaging helps in assessing patients with risk factors that increase the risk of lymph node metastasis and also helps in detection of enlarged or suspicious nodes. Magnetic resonance imaging (MRI) has been found to have an

accuracy of 74% in determining the depth of myometrial invasion, though the presence of large polypoidal tumors, small sized uterus, and fibroids may limit the assessment in some cases [25, 26]. The MRI also helps determine cervical invasion and nodal disease, if any. PET-CECT has moderate sensitivity (78–79%) with good specificity (98–99%) and negative predictive value (95–97%) in identifying nodal involvement but cannot identify low-volume disease [27]. The role of PET scans in early cancers is limited as they add to the cost and often do not change the management.

5.2.4 Sentinel Lymph Node Mapping

Sentinel lymph node (SLN) mapping is based on the premise that if the sentinel node or the first draining lymph node is negative for disease, metastatic disease in the remaining non-enlarged nodes of the nodal basin can be ruled out with reasonable certainty. Hence, complete lymph node dissection can be avoided, providing the same diagnostic and prognostic information, while minimizing the morbidity. SLN mapping is validated for clinical stage I, uterine-confined endometrial cancer.

Due to the complexity of lymphatic drainage of the endometrium, there has been much debate on the best suited injection site for identifying sentinel nodes with maximum accuracy. Different techniques of dye or tracer injection have been evaluated—cervical, sub-serosal fundal, deep myometrial, and hysteroscopy guided subendometrial. The cervical injection technique is easy and has provided the best sentinel lymph node detection rates. Cervical injection of the dye provides excellent access to uterine lymphatics (superficial subserosal, intermediate stromal, and deep submucosal) confluencing in the parametria which lead into the pelvic and occasionally the para-aortic sentinel lymph nodes. Some lymphatics which run from the uterus into the para-aortic nodes directly via the infundibulopelvic ligaments are accessed through deep cervical injections but the accuracy of mapping para-aortic sentinel nodes by the cervical technique has not been comprehensively investigated. The dye or tracer is injected into the superficial (1-3 mm) and deep (1–2 cm) cervical tissue at 3 and 9 o'clock [2]. It should be injected slowly to increase the lymphatic uptake and minimize staining of deep pelvic tissues. The retroperitoneal spaces are then opened on both sides and the sentinel lymphatic pathways emanating from the parametria are traced. The most proximal lymph nodes in the sentinel pathway are then excised and sent for pathological assessment.

The most common site of sentinel lymph node in endometrial cancer is in the superior obturator region of pelvic nodal basin. Less commonly, the node is detected in the common iliac or presacral region [2]. FIRES trial (Fluorescence Imaging for Robotic Endometrial Sentinel lymph node biopsy), a prospective randomized study aimed to study the accuracy of sentinel lymph node mapping, found sentinel nodes in the following regions: external iliac (38%), obturator (25%), inframesenteric para-aortic (14%), internal iliac (10%), common iliac (8%), presacral (3%), infrarenal para-aortic (1%), and others (including parametrium 1%) [28]. Approximately 5% of SLNs in endometrial cancer are found in areas not routinely dissected with

the standard lymphadenectomy templates, such as presacral or deep internal iliac lymph nodes [2]. In the FIRES trial, SLN mapping found positive nodes outside the traditional surgical boundaries in 20% of the patients [28].

Various tracers have been used for sentinel lymph node mapping in endometrial cancer. These include colored dyes (Isosulfan Blue 1%, Methylene Blue 1%, and Patent Blue 2.5%), radiocolloid technetium-99 m (Tc-99 m) and indocyanine green (ICG). Colorimetric lymphatic mapping employs dyes like isosulfan blue and methylene blue which are injected into the cervix and then blue-colored sentinel nodes and lymphatics are identified in the retroperitoneum within 10–20 minutes. This approach can be used in open, laparoscopic, and robotic staging. Delay from cervical injection to mapping should be avoided to prevent low detection rates due to transit of dye through the sentinel node [4]. The advantages of using colored dyes is that it does not require any costly equipment. Disadvantages include a small risk (1%) of allergic reaction especially in patients with history of asthma or multiple allergies [29], paradoxical methemoglobinemia, and interference with the measurement of oxygen saturation leading to falsely low oxygen saturation readings, and lower detection rates when used alone (as opposed to when used in combination with radioisotope).

The radiometric method of sentinel node mapping uses technetium-99 with nuclear imaging and intraoperative gamma counters to detect nodes, often in combination with blue dyes to increase the detection rate. One milliliter of 1 mCi of Tc-99 m is injected, generally 1 day prior to surgery. A gamma probe identifies areas of "hot" tracer signal intraoperatively based on audiometric signals. The areas of increased gamma signal are dissected to visually identify blue nodes and then the gamma probe is used to identify the signal strength of these nodes. Nodes which are hot and/or blue are mapped as sentinel nodes. The advantage of using both dyes and Tc-99 is that while the blue dye helps in visually localizing the representative node, the radioisotope penetrates through deep tissue and fatty nodal basins, thereby increasing the detection of sentinel lymph nodes [4]. Preoperative lymphoscintigraphy or three-dimensional single photon emission computed tomography with integrated CT (SPECT/CT) can be used along with the radiometric method in order to identify the location of sentinel lymph nodes prior to surgery.

Near-infrared (NIR) method came into use after the colorimetric and radiometric procedures. It uses indocyanine green (ICG), a tricarbocyanine dye which shows florescence when seen through a near-infrared light (range, 700–900 nm). Near-infrared imagers are required to receive the 830 nm wavelength emitted by ICG and visualize its drainage into the lymphatic vessels and these are available at present for laparotomy, laparoscopic, and robotic procedures (Fig. 5.2). A concentration of 0.5–1.25 mg/mL is generally used. The advantage of indocyanine green is that not only does it allow real-time visualization during sentinel node mapping, the signal also penetrates deep tissue, hence combining the positives of colorimetric and radiometric techniques. ICG is superior to blue dyes in obese patients and has higher overall and bilateral detection rates in comparison to even combined (blue dye plus Tc-99) methods. It also has a better safety profile than blue dyes (anaphylaxis, skin necrosis) and Tc-99 m (radioactivity) and the risk of adverse events is extremely

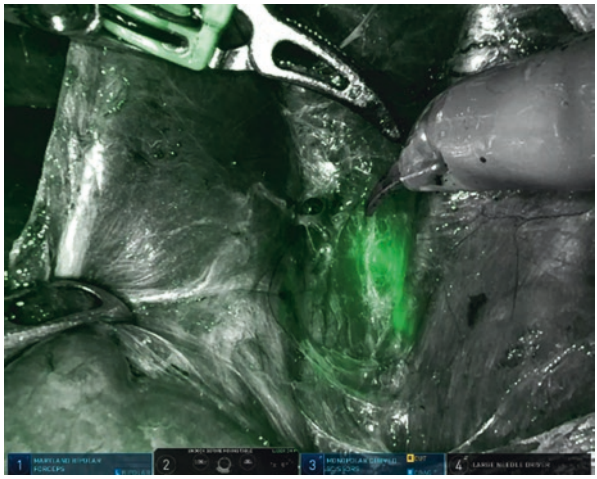


Fig. 5.2 Sentinel lymph node mapping using indocyanine green

low (1/42,000 for anaphylaxis) [4]. Even so, it should be avoided in patients with severe iodine allergy and in liver failure, as it is excreted completely by the liver. The disadvantage of ICG is that expensive NIR imaging equipment is required with this method. Due to the high SLN detection rate, ICG is commonly used in many centers at present.

In order to maximize the rates of successful SLN mapping, it is imperative to follow the NCCN SLN algorithm, which recommends side-specific nodal dissection in cases of failed mapping and removal of any suspicious or grossly enlarged nodes regardless of mapping (Fig. 5.3). Close adherence to this algorithm has been found to have less than 5% false-negative rate in detecting nodal metastasis. The Society of Gynecologic Oncology (SGO) recommends that surgeons should perform at least 20 SLN procedures with concomitant completion lymphadenectomy prior to adopting SLN algorithm for routine management of early endometrial cancers [4]. Abu Rustum et al. reported a learning curve with an increase in SLN detection from 77% to 94% ($p = 0.03$) over 30 cases [30, 31].

Sentinel lymph node biopsy is combined with ultrastaging to increase the detection of nodal metastasis, especially low volume disease not detected on routine histology. Ultrastaging involves serial sectioning and combined hematoxylin and eosin (H&E) staining with immunohistochemistry which improves the accuracy of detecting micrometastases. Though there are no formal guidelines for pathologic assessment of sentinel nodes in endometrial cancer, the Memorial Sloan Kettering Cancer Center (MSKCC) group proposes initial evaluation by routine H&E, and if negative, cut two adjacent 5-μm sections (one H&E and one cytokeratin AE1/AE3) from each paraffin block 50 μm apart [32]. By increasing the detection of metastatic disease, ultrastaging can lead to upstaging in 5–15% of patients. A retrospective study of 780 patients undergoing SLN mapping with lymphadenectomy compared with lymphadenectomy alone showed that SLN mapping detected more metastasis (30.3% vs 14.7%; $P < 0.001$) and was associated with greater use of adjuvant therapy [33].

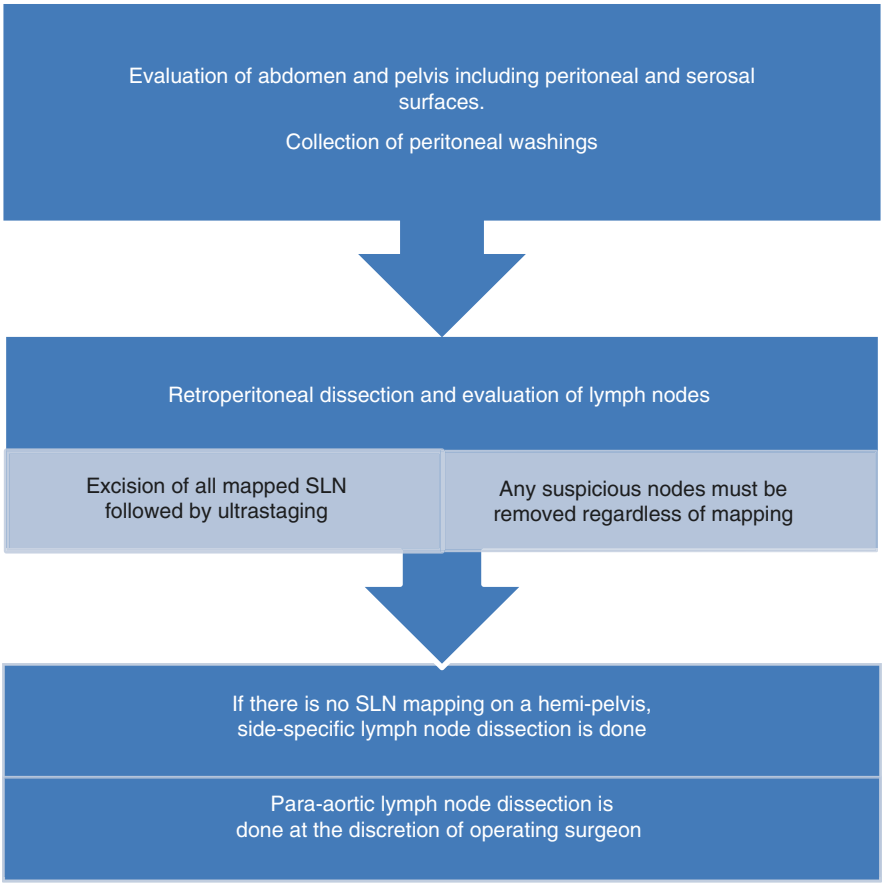


Fig. 5.3 The SLN algorithm for surgical staging of endometrial cancer [2] (Courtesy of Dr. Nadeem R. Abu-Rustum at Memorial Sloan Kettering Cancer Center)

Low-volume metastases accounts for approximately half of the lymph node metastases detected through sentinel node ultrastaging in endometrial cancer [33]. Although most patients with micrometastases or isolated tumor cells (ITCs) detected on SLN ultrastaging receive adjuvant treatment, it is uncertain what impact this treatment has on the survival outcomes, and the prognosis and appropriate management of these cases is not yet clear. In a retrospective analysis of 844 patients with endometrial cancer undergoing SLN mapping, 3 year recurrence-free survival was almost similar for patients with negative SLNs, ITCs, and micrometastasis—90% for those with negative SLNs, 86% for ITCs, and 86% for micrometastasis but significantly lower—71% ($p < 0.001$) for those with SLN macrometastasis [34].

The accuracy of SLN mapping in endometrial cancer has improved progressively over the years. A recent meta-analysis of 48 studies, including 5348 patients, reported that the pooled SLN detection rates were 87% (95% CI: 84–89%, 44 studies) for

overall detection and 61% (95% CI: 56–66%, 36 studies) for bilateral detection. Indocyanine green use was associated with improved overall (94%, 95% CI: 92–96%, 19 studies) SLN detection rates compared to blue tracer (86%, 95% CI: 83–89%, 31 studies) or technetium-99 (86%, 95% CI: 83–89%, 25 studies). There was no difference in para-aortic SLN detection rate between each tracer. The pooled estimates from 34 studies showed a 94% sensitivity and 100% negative predictive value (NPV). Diagnostic accuracy of SLN mapping was not negatively affected in patients with high-grade endometrial histology [35]. A comparative analysis between complete lymphadenectomy at the Mayo Clinic and the SLN algorithm at MSKCC showed pelvic node metastases in 2.6% and 5.1% of patients, respectively ($p = 0.03$), and para-aortic node metastases in 1.0% and 0.8%, respectively ($p = 0.75$). Though there were some differences in the patient characteristics and adjuvant therapy in both groups, the 3-year disease-free survival rates were similar—96.8% [95% CI, 95.2–98.5] and 94.9% [95% CI, 92.4–97.5], respectively [36].

The FIRES trial, a multicenter, prospective, cohort study published in 2017 was designed to evaluate the sensitivity and negative predictive value of SLN mapping and compare it with the gold standard of complete lymphadenectomy in detecting metastatic disease for endometrial cancer. Patients with clinical stage 1 endometrial cancer of all grades and histologies undergoing robotic staging received an intracervical injection of ICG dye with sentinel-lymph-node mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Of the 385 patients enrolled in the trial, 340 underwent SLN mapping with complete lymphadenectomy with 58% of these having para-aortic lymphadenectomy. Eighty-six percent of patients had successful mapping of at least one sentinel lymph node. The sensitivity to detect node-positive disease using SLN mapping was 97.2% (95% CI, 85–100), and a negative predictive value of 99.6% (95% CI, 97.9–100). The authors concluded that SLN biopsy has a high degree of accuracy in detecting endometrial cancer metastases and even though it may not identify metastases in 3% of patients with node-positive disease, it can safely replace complete lymphadenectomy in staging of endometrial cancer [28].

SLN mapping has been controversial in patients with high-risk histology (serous carcinoma, clear cell carcinoma, carcinosarcoma) but promising results have been reported recently [2, 4]. The FIRES trial study group included 28% patients with high-grade histologies, but the role of SLN biopsy in this subset has not been addressed definitively. The one false-negative result in the study was in a patient with a high-grade (serous) cancer [28].

One important issue with SLN detection using cervical injection of dyes is the lower rates of para-aortic SLN detection compared to fundal or intra-tumoral injection techniques. Failure to identify metastasis in para-aortic nodes would result in failure to prescribe the necessary adjuvant treatment, thereby affecting the outcomes of the disease. In the FIRES trial, there were no cases of missed isolated para-aortic nodal metastases among patients who mapped at least one SLN and underwent para-aortic lymphadenectomy. In order to avoid missing metastatic disease in the para-aortic region, preoperative imaging must be done for patients with high-grade tumors who are at a high risk for lymph node metastases, in order to detect any

suspicious para-aortic lymph nodes. These nodes should be removed during surgery regardless of SLN mapping. In addition, frozen section should be employed intraoperatively to detect high-risk factors in the uterine specimen (high-grade histology, deep myometrial invasion), if any, and pelvic nodal metastasis to identify patients at high risk for para-aortic disease. During the surgery, the surgeon should carefully inspect the para-aortic region for identification of SLNs, especially in cases where no pelvic SLN could be mapped on one or both sides. Furthermore, patients with high-grade histologies, more than 50% myometrial invasion and positive pelvic nodes should undergo para-aortic lymphadenectomy, and the SLN algorithm should be used only for pelvic nodal evaluation [4].

Routine frozen section of SLNs is not advocated because of the low sensitivity of frozen for detection of metastasis in normal appearing lymph nodes. Also, frozen section may distort the nodal tissue precluding the ultrastaging to detect low volume disease. In cases where SLNs are found positive on final histology and ultrastaging, completion lymphadenectomy has little role as it does not change further management, nor is it therapeutic in clinically normal nodes. Postoperative imaging is advised in these cases to ensure there are no gross bulky residual nodes that were missed during initial staging and these are the only cases that may benefit from surgical cytoreduction. Imaging also helps guide adjuvant treatment including radiotherapy and deciding the dosing and fields of radiation with extended radiation to the para-aortic region for patients with proximal iliac SLN metastases, positive para-aortic findings on imaging, or high-grade cancers.

The SGO has laid forth the following recommendations for SLN mapping in endometrial cancer [4]:

1. Cervical injection of tracers detects pelvic lymph node metastasis accurately and has a low (<5%) false-negative rate when the NCCN SLN algorithm is strictly adhered to. Completion lymphadenectomy should be done by the surgeon before adopting the algorithm into clinical practice until he or she can elicit similar rates of SLN detection as documented in current literature and with a <5% false-negative rate.
2. Cervical injection of ICG dye with infrared imaging is preferable for SLN mapping whenever available, because of the technical ease and high rates of successful SLN detection. Radiocolloid Tc-99 combined with blue dye is also an acceptable approach when ICG is not available.
3. SLN mapping using the NCCN SLN algorithm can be performed in place of systematic pelvic lymphadenectomy for women with uterine confined grade1 and 2 endometrioid cancers.
4. SLN mapping along with ultrastaging increases the detection of nodal metastasis compared to routine lymphadenectomy. Patients should be counseled regarding the small (<5%) risk for missing metastatic disease with SLN biopsy.
5. SLN mapping is accurate in detecting pelvic nodal metastasis and also detects some para-aortic SLNs. The decision about performing para-aortic nodal dissection is at the surgeon's discretion and based on high-risk factors like high-grade histology, deep uterine invasion, and positive pelvic nodes.

6. Pathologic processing of each SLN should be done by serial sectioning at 2-mm intervals along the longitudinal plane of the node, and microscopic examination of all slices with at least one representative H&E level. Ultrastaging increases the detection of ITCs and micrometastasis, but the clinical significance of ITCs is currently uncertain.
7. The NCCN SLN algorithm can be incorporated into the staging of high-grade endometrial cancer (grade 3 endometrioid, serous, clear cell, or carcinosarcoma) and is currently being used by various institutions, with encouraging early results. But until more data regarding the accuracy and safety of SLN biopsy in this group of patients becomes available, completion lymphadenectomy with para-aortic assessment is advisable in these cases.

5.3 Conclusions

Therapeutic role of lymphadenectomy in patients with negative nodes is debatable but there is definite clinical benefit in debulking enlarged nodes. Selective use of lymphadenectomy has been advocated in early-stage endometrial cancer to avoid overtreatment in low-risk cases and reduce the morbidity associated with systematic lymph node dissection without compromising survival outcomes. This can be done by appropriate patient selection—doing lymphadenectomy in cases at high risk for nodal metastasis but avoiding it in low-risk cases. Sentinel lymph node assessment is feasible in uterine confined disease and may eliminate the need for complete lymphadenectomy in low-risk patients. The question of whether lymphadenectomy has a therapeutic benefit in high-risk endometrial cancer could be answered by a prospective randomized trial comparing sentinel lymph node assessment to complete pelvic and para-aortic lymphadenectomy in this group.

Key Points

- The standard management of early-stage endometrial cancer includes surgical staging which comprises total hysterectomy, bilateral salpingo-oophorectomy, and lymph node assessment. Complete lymphadenectomy includes both pelvic and para-aortic lymph node assessment.
- Lymphadenectomy has a definite therapeutic benefit and is associated with improved survival outcomes with debulking clinically enlarged nodes or nodal macrometastasis, and possibly with resection of microscopic metastasis. The therapeutic role of lymphadenectomy in node-negative patients is debatable.
- Previous guidelines including older NCCN recommendations recommended complete pelvic and para-aortic lymph node assessment in all patients of endometrial cancer, irrespective of risk factors. The current guidelines recommend selective use of lymphadenectomy in early-stage endometrial cancer as it can reduce the morbidity associated with lymph node dissection without compromising clinical outcomes, and avoid overtreatment in low-risk cases (Stage IA, grade 1 or 2).

- In patients with grade 1 to 2 endometrioid tumors, less than 50% myometrial invasion, and tumor size less than 2 cm, the risk of lymph node metastasis is very low (Mayo's criteria). Lymphadenectomy can be avoided in this low-risk group.
- Patients with grade 3 endometrioid tumors and more than 50% myometrial invasion, and those with high-risk histologies (serous carcinoma, clear cell carcinoma, carcinosarcoma) should undergo both pelvic and para-aortic lymph node assessment.
- Sentinel lymph node (SLN) mapping is validated for uterine confined grade1 and 2 endometrioid cancers. The preferred technique is cervical injection at 3 and 9 o'clock using indocyanine green dye. The SLN algorithm proposed by the NCCN has shown high rates of successful SLN mapping with very low (<5%) false-negative rates. Side-specific nodal dissection should be done in cases of failed mapping and any suspicious or grossly enlarged nodes should be removed regardless of mapping.

References

1. Abu-Rustum NR, Alektiar K, Iasonos A, et al. The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: a 12-year experience at Memorial Sloan-Kettering Cancer Center. Gynecol Oncol. 2006 Nov;103(2):714–8.
2. Koh WJ, Abu-Rustum NR, Bean S, et al. Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2018 Feb;16(2):170–99.
3. Barlin JN, Khoury-Collado F, Kim CH, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: beyond removal of blue nodes. Gynecol Oncol. 2012 Jun;125(3):531–5.
4. Holloway RW, Abu-Rustum NR, Backes FJ, et al. Sentinel lymph node mapping and staging in endometrial cancer: a Society of Gynecologic Oncology literature review with consensus recommendations. Gynecol Oncol. 2017 Aug;146(2):405–15.
5. 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;109:11–8.
6. Mariani A, Keeney GL, Aletti G, et al. Endometrial carcinoma: paraaortic dissemination. Gynecol Oncol. 2004;92:833–8.
7. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer A Gynecologic Oncology Group Study. Cancer. 1987;60(8 Suppl):2035–41.
8. Abu-Rustum NR, Gomez JD, Alektiar KM, et al. The incidence of isolated paraaortic nodal metastasis in surgically staged endometrial cancer patients with negative pelvic lymph nodes. Gynecol Oncol. 2009;115:236–8.
9. Case AS, Rocconi RP, Straughn JM, et al. A prospective blinded evaluation of the accuracy of frozen section for the surgical management of endometrial cancer. Obstet Gynecol. 2006;108:1375–9.
10. Havrilesky LJ, Cragun JM, Calingaert B, et al. Resection of lymph node metastases influences survival in stage IIIC endometrial cancer. Gynecol Oncol. 2005;99:689–95.
11. Bristow RE, Zahurak ML, Alexander CJ, et al. FIGO stage IIIC endometrial carcinoma: resection of macroscopic nodal disease and other determinants of survival. Int J Gynecol Cancer. 2003;13:664–72.
12. 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;56:29–33.

13. Cragun JM, Havrilesky LJ, Calingaert B, et al. Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. J Clin Oncol. 2005;23:3668–75.
14. Todo Y, Kato H, Kaneuchi M, et al. Survival effect of Para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet. 2010;375:1165–72.
15. 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;107:1823–30.
16. Polterauer S, Khalil S, Zivanovic O, et al. Prognostic value of lymph node ratio and clinicopathologic parameters in patients diagnosed with stage IIIC endometrial cancer. Obstet Gynecol. 2012 Jun;119(6):1210–8.
17. ASTEC Study Group, Kitchener H, Swart AM, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet. 2009;373:125–36.
18. Benedetti Panici P, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst. 2008;100:1707–16.
19. Frost JA, Webster KE, Bryant A, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 2017 Oct 2;10:CD007585.
20. Bogani G, Dowdy SC, Cliby WA, et al. Role of pelvic and paraaortic lymphadenectomy in endometrial cancer: current evidence. J Obstet Gynaecol Res. 2014;40:301–11.
21. AlHilli MM, Podratz KC, Dowdy SC, et al. Preoperative biopsy and intraoperative tumor diameter predict lymph node dissemination in endometrial cancer. Gynecol Oncol. 2013;128:294–9.
22. Franchi M, Ghezzi F, Melpigano M, et al. Clinical value of intraoperative gross examination in endometrial cancer. Gynecol Oncol. 2000;76:357–61.
23. Goff BA, Riche LW. Assessment of depth of myometrial invasion in endometrial adenocarcinoma. Gynecol Oncol. 1990;38:46–8.
24. Colombo N, Preti E, Landoni F, et al. Endometrial cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013;24(Suppl. 6):33–8.
25. Hricak H, Rubinstein LV, Gherman GM, et al. MR imaging evaluation of endometrial carcinoma: results of an NCI cooperative study. Radiology. 1991;179:829–32.
26. 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;194:567–72.
27. Signorelli M, Guerra L, Buda A, et al. 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. 2009;115:231–5.
28. Rossi EC, Kowalski LD, Scalici J, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 2017 Mar;18(3):384–92.
29. Albo D, Wayne JD, Hunt KK, et al. Anaphylactic reactions to isosulfan blue dye during sentinel lymph node biopsy for breast cancer. Am J Surg. 2001 Oct;182(4):393–8.
30. Abu-Rustum NR, Khoury-Collado F, Pandit-Taskar N, et al. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? Gynecol Oncol. 2009 May;113(2):163–9.
31. Khoury-Collado F, Glaser GE, Zivanovic O, et al. Improving sentinel lymph node detection rates in endometrial cancer: how many cases are needed? Gynecol Oncol. 2009 Dec;115(3):453–5.
32. Kim CH, Soslow RA, Park KJ, et al. Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. Int J Gynecol Cancer. 2013 Jun;23(5):964–70.
33. Holloway RW, Gupta S, Stavitzski NM, et al. Sentinel lymph node mapping with staging lymphadenectomy for patients with endometrial cancer increases the detection of metastasis. Gynecol Oncol. 2016 May;141(2):206–10.
34. St Clair CM, Eriksson AG, Ducie JA, et al. Low-volume lymph node metastasis discovered during sentinel lymph node mapping for endometrial carcinoma. Ann Surg Oncol. 2016 May;23(5):1653–9.

35. How JA, O'Farrell P, Amajoud Z, et al. Sentinel lymph node mapping in endometrial cancer: a systematic review and meta-analysis. Minerva Ginecol. 2018 Apr;70(2):194–214.
36. Zahl Eriksson AG, Ducie J, Ali N, et al. Comparison of a sentinel lymph node and a selective lymphadenectomy algorithm in patients with endometrioid endometrial carcinoma and limited myometrial invasion. Gynecol Oncol. 2016 Mar;140(3):394–9.

Sentinel Node Mapping in Endometrial Cancer

6

Anupama Rajanbabu and Reshu Agarwal

6.1 Introduction

Endometrial cancer is the most common gynecologic cancer in North America, and worldwide there are approximately 320,000 cases diagnosed annually [1]. Following the Federation of International Gynecology and Obstetrics (FIGO) adoption of surgical staging in 1988, pathology that includes information about the primary tumor, as well as lymph node status, has guided prognosis and use of adjuvant therapies [2]. Surgical staging is associated with risks of lymphedema, lymphocysts, cellulitis, and damage to nearby nerves.

Sentinel lymph node (SLN) assessment has been proposed as a more "targeted" alternative to complete pelvic lymphadenectomy in an effort to secure information about lymph node status for treatment planning, yet minimize collateral damage.

6.2 Importance of Lymph Node Assessment

There are three potential roles of LN assessment in endometrial cancer:

1. To assign a surgical stage and provide prognostic information.
2. To treat patients with positive nodes.
3. To direct adjuvant radiation.

A. Rajanbabu (✉)
Department of Gynecologic Oncology, Amrita Institute of Medical Sciences, Kochi, Kerala, India

R. Agarwal
Department of Gynecologic Oncology, Prakhar cancer Centre, Kanpur, Uttar Pradesh, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_6

In 1988, the FIGO Committee on Gynecology Oncology replaced the clinical staging of endometrial cancer with the surgical staging and again revised in 2009 [2, 3]. This change in staging was done in response to the GOG studies of 1970s and early 1980s, which demonstrated a high incidence of lymph node metastases in high-risk cases [4].

Ninety percent of women with endometrial cancer present with early-stage disease, confined to the uterus (stage I) [5]. The 5-year overall survival rate in this patient population is 80% to 90% [6, 7]. Approximately 10% to 15% of these patients will, in fact, have metastatic nodal disease [8]. Nearly, 15% of patients will be deemed to have grade 1 tumors on preoperative office biopsy or dilatation and curettage will actually have a higher-grade disease on final pathologic review after hysterectomy [9]; therefore, it is of utmost importance to stage and treat these patients properly and avoid missing undetected metastatic disease that may upstage the patient [10].

Proper surgical staging (total hysterectomy, bilateral salpingo-oophorectomy, peritoneal washing, and lymph node assessment), the most important prognostic factor, provides information on the actual extent of disease rather than on perceived risks based on uterine factors such as tumor size, grade, histology, and depth of myometrial invasion. Documentation of positive nodes identifies a high-risk population to tailor adjuvant treatment. Nodal resection also allows identification of node-negative patients, potentially reducing the need for external beam radiotherapy [11].

6.3 Road to SLN Mapping in Endometrial Cancer

Despite the revision of the FIGO staging system for endometrial cancer, the adoption of comprehensive surgical staging of pelvic and para-aortic nodes has not been universal and the extent of appropriate lymph node dissection for early-stage and low-grade disease has been controversial [12].

Routine, systematic lymphadenectomies are not without complications and have been associated with increased risk of blood vessel and nerve damage, lymphedema and lymphocyst formation [13, 14]. In a study of 1289 patients with uterine corpus malignancy at Memorial Sloan Kettering Cancer Centre, 16 (3.4%) of 469 patients who had 10 or more lymph nodes removed at surgery developed new postoperative symptomatic leg lymphedema [15].

The two large randomized European trials were conducted to evaluate the impact of routine lymphadenectomy on survival [16, 17]. Benedetti Panici et al. identified approximately 10% more cases of nodal metastasis with the inclusion of lymphadenectomy. However, despite the increased detection of metastasis, there was no survival advantage and a significantly higher rate of lymphedema was documented in staged patients [16]. These observations were consistent with the results of the ASTEC trial, which also showed no survival benefits and an increase in lymphedema [17]. These trials were criticized for lacking a standardized lymphadenectomy protocol, as well as for inconsistencies in adjuvant therapy. Nonetheless, these phase 3 trials legitimately called into question the role of routine lymphadenectomy in endometrial cancer.

The retrospective study on Survival Effect of Para-Aortic Lymphadenectomy (SEPAL) in endometrial cancer showed significantly improved overall survival in select intermediate- and high-risk patients undergoing pelvic and para-aortic lymph node dissection [18]. However, the median number of nodes removed was much larger than in most studies, and it was difficult to determine whether survival benefit was a result of the para-aortic nodes or of the adjuvant chemotherapy [18].

In view of the controversial role of comprehensive routine lymphadenectomies and the morbidity associated, some surgeons chose to remove only clinically suspicious enlarged LNs, and rather than triage care based on lymph node involvement, the need for adjuvant treatment is based on the "uterine risk factors" for LN metastasis and recurrence. However, this minimalist approach of assessing patients' probability of LN involvement based on uterine factors does make patients prone to over- or under-treatment of disease [12].

Another pathway to lymph node assessment is selective lymphadenectomy where surgeons decide to perform lymphadenectomies based on intra-operative assessment of grade and depth of myometrial invasion. Critics of selective lymphadenectomy argue against the accuracy of frozen section and inadequate staging of women with advanced cancer [19].

Mariani et al. defined a "low-risk" population based on histologic criteria from GOG 33 and their own historical cohort, in whom staging lymphadenectomy may be safely omitted [20]. Low risk was defined as grade 1 or 2 disease, less than 50% myometrial invasion, and tumor diameter less than 2 cm. These criteria were then used in a prospective observational study that demonstrated patients with low-risk disease (approximately 30% of all the endometrial cancers treated at the Mayo Clinic) had a less than 1% risk of having a positive lymph node or nodal recurrence, compared to a 16% risk of lymph node involvement for endometrioid adenocarcinoma that did not meet these criteria [20]. The Mayo Clinic's low-risk group represents a clinically significant number of women who may be able to avoid staging lymphadenectomy. However, the diagnosis depends on intraoperative frozen section, a practice that has variable levels of reported accuracy [21, 22] and may potentially lead to understaging some high-risk cases. In contrast, patients with high-grade histologies (endometrioid grade 3, clear cell, serous, and carcinosarcoma) have a 20–40% risk of lymph node involvement [20, 23]. Although intraoperative frozen section has been shown to accurately triage patients with high-risk uterine features to lymphadenectomy at some institutions, the generalizability of this method is limited by poor reproducibility outside of expert centers [20–22]. Some studies reporting a discordance rate of histological grade and depth of myometrial invasion on intraoperative frozen section as high as 46% [19, 22], whereas other studies as low as 3% [24, 25].

In view of these challenges, sentinel lymph node (SLN) mapping has emerged as a viable alternative to the systematic lymphadenectomy in patients with endometrial cancer. The logic of the SLN approach lies in targeting the "correct" nodes, or those most likely to harbor disease based on lymphatic flow, rather than removing a greater number of nodes to perform thorough staging. Ultimately, the end goal of both approaches is adequate staging.

6.4 Sentinel Lymph Node Mapping

The concept of sentinel lymph node is based on the orderly progression of lymphatic metastases. Important assumptions about the value of SLN mapping can be found in Table 6.1.

A sentinel lymph node is the first node or group of nodes draining the primary tumor site/organ. In most cases, a dye is injected into (or near) the organ where malignancy developed. The lymphatic distribution of the organ is then mapped, allowing the SLN to be identified, excised, and examined for evidence of metastatic disease. The technique of lymphatic mapping and sentinel lymph-node biopsy has improved surgeons' ability to detect small-volume disease in lymph nodes while greatly reducing intraoperative and postoperative morbidity.

The success story of SLN mapping began in 1977 with the first report on lymphangiography of penis [26]. However, the wide acceptance of technique was not reached until the late 1980s with the introduction of blue dye and radiocolloid SLN mapping technique in patients with cutaneous melanoma [27]. Results of large randomized NSABP B-32 trial on breast cancer patients, further established the role of SLN mapping technique in solid malignancies with an acceptable false-negative rate of 9.8%, and no survival difference [28].

In gynecology oncology, SLN mapping first reached acceptance for the management of vulval cancer. The GROINSS-V1 trial demonstrated an acceptable recurrence risk and has effectively established SLN mapping as the standard of care for the management of clinically node-negative T1–T2 ($\leq$4 cm) vulval cancer [29].

Burke et al. first reported the use of SLN mapping in endometrial cancer in 1996 [30]. Following the leadership by the group at Memorial Sloan Kettering Cancer Centre (MSKCC), there have been a plethora of published studies with numerous different methodologies that have been reported. More recently, it has been incorporated into the National Comprehensive Cancer Network (NCCN) treatment guidelines for the assessment of lymph nodes in select patients with vulval, endometrial, and cervical cancers [8, 31, 32]. The appeals of SLN mapping lies in the possible avoidance of "overstaging" via lymph node dissection of normal/negative nodes and enhanced precision in finding micrometastasis with pathologic ultrastaging of SLNs.

Table 6.1 Assumptions of SLN mapping

1.	A tumor's lymphatic drainage is methodical and predictable. Thus the first (or sentinel) lymph node is a lymphatic chain will contain metastasis if present anywhere.
2.	A marker when injected into a site that mimics the tumors' lymphatic drainage, should permit the SLN's identification with appropriate sensitivity and specificity.
3.	Inability to identify a SLN does not imply negative lymph node status. Failure to identify a SLN should be considered a mapping failure and, thus, should be managed with systematic lymphadenectomy.

6.4.1 Nodal Stations in Endometrial Cancer

The lymphatic system of the corpus uteri is formed by three main lymphatic trunks: utero–ovarian (infundibulopelvic), parametrial, and presacral. They collectively drain into the hypogastric (also known as internal iliac), external iliac, common iliac, presacral, and para-aortic nodes. Direct metastases to the para-aortic lymph nodes are uncommon. This is surprising given that a direct route of lymphatic spread from the corpus uteri to the para-aortic nodes through the infundibulopelvic ligament has been suggested from anatomical and sentinel lymph node studies.

6.4.2 Mapping Techniques for Endometrial Cancer

6.4.2.1 Injection Sites

Three different types of SLN mapping techniques exist based on the site of injection:

1. Cervix (Fig. 6.1)
2. Subserosal uterine fundus and deeper myometrium
3. Hysteroscopically guided subendometrial tumor injections

The three techniques have been described with varying lymphatic distribution and SLN detection rates in several observation studies [33–37]. Although the subserosal and the subendometrial techniques offer higher rates of para-aortic SLN detection [38], cervical injection has become the most favored technique, as it is straightforward and garners the highest SLN detection rates [9, 39]. The tracer is

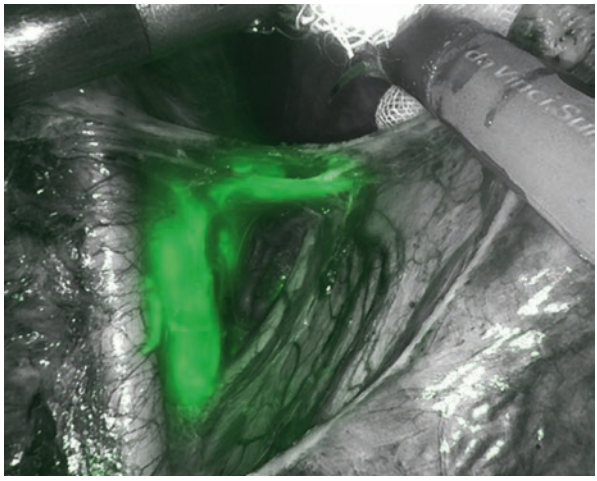


Fig. 6.1 Left external iliac sentinel node showing fluorescence under NIR light. The lymphatic track from the site of injection to the sentinel node is also seen

injected slowly into the submucosa or superficial cervical stroma to maximize lymphatic uptake and minimize staining of deep pelvic tissues. Available evidence suggests that cervical injection preserves the accuracy of the detection of pelvic metastatic disease [40, 41].

In a large meta-analysis, Kang et al. reported a decrease in SLN detection rates and sensitivity with the omission of cervical injection [42]. These investigators also recommended that the subserosal injection only technique be avoided because of decreased sensitivity. Based on these data, the Society of Gynecologic Oncology (SGO) has confirmed the importance of cervical injection in the consensus recommendation on sentinel lymph node mapping and staging in endometrial cancer [1].

6.4.2.2 Injection Methods and Dyes

Colorimetric Methods Colorimetric lymphatic mapping refers to the visual detection of lymph channels and nodes using colored dyes in white light. This technique requires the least complex equipment and is applicable to open, laparoscopic, and robotic approaches.

Isosulfan blue is FDA approved for lymphatic mapping. Typically, 3–5 cc of a 1% solution is injected into the cervix, after which there is immediate uptake of the dye into lymphatic channels and accumulation in the SLNs within 10–20 minutes. Delay from injection to mapping can cause low detection rates due to transit of dye through the node [43]. Injection should be superficial to minimize uptake of dye into deeper tissues. Disadvantages of isosulfan blue include its expense, limited availability, and the risk (1.1%) of allergic reaction (anaphylaxis) [44].

Methylene blue is a less expensive alternative to isosulfan blue. This is an off-label use of the dye. Evidences suggest equivalency for SLN mapping in other cancers [45]. Injection dose is 2 to 4 cc of a 1% solution.

Radionuclear Method The injection of radiolabeled colloid technetium 99 (Tc99) and detection with nuclear imaging and/or intraoperative gamma counters is one of the original techniques of SLN mapping utilized in breast, melanoma, and vulvar cancer management [46–48]. It is often used in synergy with a blue dye (or indocyanine green [ICG]) to optimize detection rates [49]. The virtue of radiolabeled isotopes is signal penetration through deep tissue, which can be advantageous in patients with endometrial cancer where nodal basins can be fatty and lymphatic drainage can be unpredictable.

A total of 1 mL of 1 mCi of Tc99 is injected. Preoperative lymphoscintigraphy to identify the number and location of SLNs [50] is optional, but requires a separate injection procedure in nuclear medicine, adding cost and inconvenience.

Near-infrared Method ICG is a water-soluble tricarbocyanine dye that emits a fluorescent signal in the near-infrared (NIR) light range. NIR imagers are filtered to receive the 830-nM wavelength emitted by ICG and visualize the ICG dye. NIR imagers are available for laparotomy, laparoscopy, and robotic surgery.

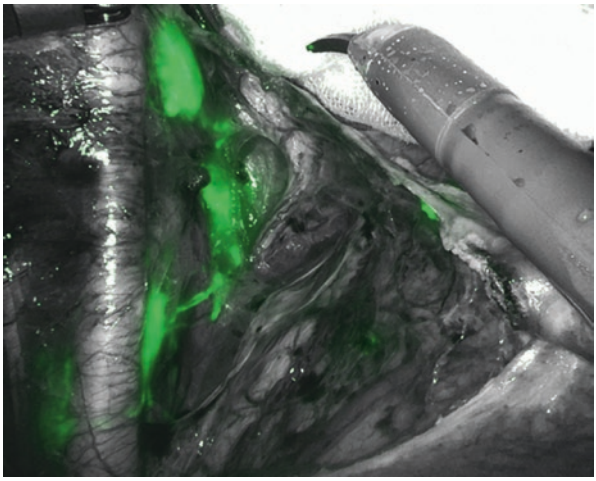


Fig. 6.2 Left obturator sentinel node with efferent lymphatic tracks going to the external iliac nodes

Optimal detection of SLNs occurs when the drug is diluted by the surgeon to a 0.5 mg/mL to 1.25 mg/mL concentration using sterile water and 2–4 mL are used [51, 52]. Papadia et al. using two different concentrations of ICG demonstrated that the higher dose of ICG was associated with the number of SLNs removed, but there was no association with the bilateral detection rate. Hence the authors concluded that the higher dose of ICG was not associated with the improved bilateral detection rate [53].

Near-infrared fluorescence for detection of sentinel lymph nodes in women with cervical and uterine cancers (FILM): a randomized, phase 3, multicenter, non-inferiority trial has demonstrated the superiority of ICG over blue dye for SLN mapping in endometrial cancer [54]. In a study of 180 endometrial cancer patients, an average of 3.1 SLNs was identified per patient. Overall and bilateral SLN detection rate with ICG was 96% and 80%, respectively, as compared to 74% and 31%, respectively, with ISB ($P < 0.001$). Fifteen patients (8.5%) were detected to have metastatic disease—all with ICG. The authors concluded ICG should become the standard dye for SLN mapping of endometrial cancer where NIR imaging technology is available.

The ICG signal penetrate tissues allowing for real-time visualization during dissection, combining the assets of colorimetric and radionuclear techniques (Figs. 6.2 and 6.3). The only disadvantage of this tracer is the requirement for specialized NIR imaging equipment. The risk of adverse events is extremely low for ICG (1/42,000 anaphylaxis); however, it should be avoided in patients with severe iodine allergy or liver failure, as it is excreted completely by the liver.

6.5 Ultrastaging of Sentinel Nodes for Endometrial Cancer

Routine pathologic evaluation of lymph nodes typically involves a single section through the largest diameter of each lymph node and subsequent staining with hematoxylin and eosin (H&E). By sampling the most significant nodes rather than the largest number of nodes, SLN mapping enables the pathologist to perform meticulous ultrastaging.

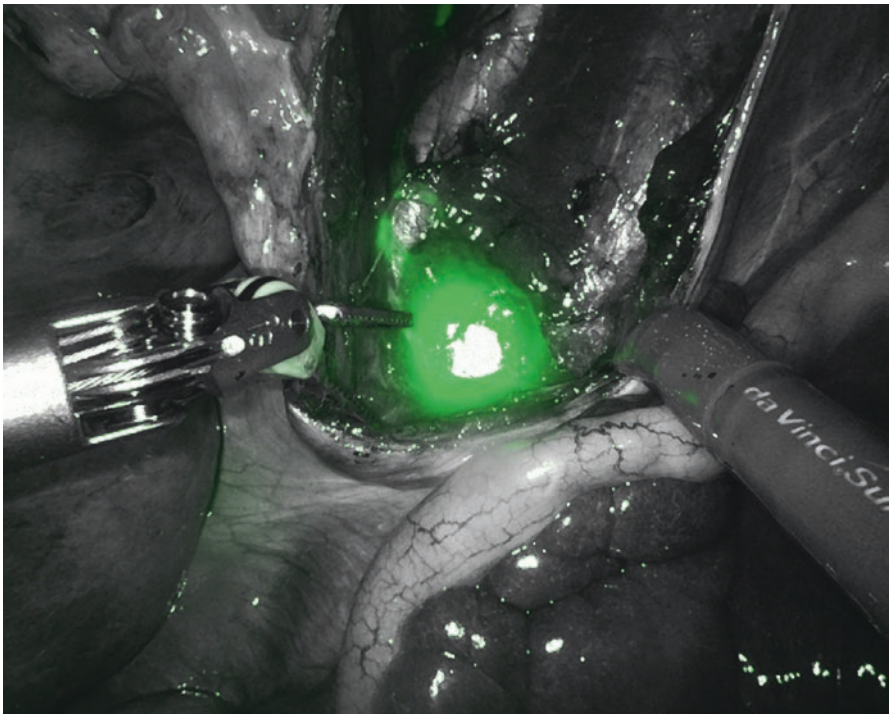


Fig. 6.3 Right common iliac sentinel node

"Ultrastaging" refers to the utilization of enhanced pathology techniques, including deeper serial sections and immunohistochemical (IHC) stains, to increase the detection of malignant cells in SLNs [55]. There are no formal evidence-based guidelines for the ultrastaging of SLNs in endometrial cancer. Hence most pathologist employ an approach used to evaluate breast cancer sentinel nodes. Additional sections are performed on SLNs negative on initial H&E at 50-μm intervals. Both H&E and anticytokeratin AE1:AE3 sections are evaluated (2 additional slides by H&E and two by AE1:AE3).

SGO consensus recommendations suggest defining metastasis according to breast cancer guidelines set forth by the American Joint Committee on Cancer (AJCC) as follows: macrometastasis (tumor cells >2.0 mm in diameter), micrometastasis (tumor cell >0.2 mm to ≤2 mm, and/or >200 cells), and isolated tumor cells (<0.2 mm in diameter, present as either single tumor cells or clusters of <200 cells; ITCs can be detected by H&E or by IHC alone) [1, 56].

Ultrastaging has been found to increase the detection of lymphatic metastasis in endometrial cancer and the subsequent upstaging [49, 57, 58]. In a large series at MSKCC, Kim et al. reviewed 508 patients who underwent SLN mapping with ultrastaging of sentinel nodes and demonstrated that ultrastaging detected 36% (23/64) of positive nodes that would have been missed on routine H&E staining, including

4 patients with micrometastasis and 19 patients with ITC. The rate of micrometastasis was 0.8% in patients with no myometrial invasion; hence the authors concluded ultrastaging could be omitted in these patients [57]. Naouro demonstrated a much higher rate of ultrastaging-detected metastasis (41%) in endometrial cancer with high-grade histology [59]. Touhami et al. proposed that the size of SLN metastasis may predict the risk of metastases in the non-SLN [59].

6.6 Status of SLN Mapping in Endometrial Cancer

Several observational studies of SLN mapping in endometrial cancer using either single dyes, combinations of dyes, or Tc-99 radiocolloid injected into the cervix have been reported [33, 35–38, 40, 49, 51, 57, 60–75]. The reproducibility of the cervical injection technique, high success rate, and low-risk for isolated aortic metastasis has led most investigators to use cervical injections of tracers [42]. ICG, with or without the other tracers injected into the cervix, used with fluorescent imaging emerged as the most consistently effective pelvic SLN detection technique in endometrial cancer [51, 60]. With the initial studies of SLN mapping by Abu-Rustum et al., a low false-negative rate was demonstrated [9]. The same investigators described a learning curve with an increase in SLN detection from 77% to 94% ($p = 0.03$) following a 30-case experience [76]. Enhanced pathologic analysis with serial sectioning and IHC increased the detection of metastasis by approximately twofold compared to routine H&E findings in patients undergoing SLN mapping, largely through the detection of micrometastases and ITCs that were not identified on the initial H&E examinations [49, 57, 58, 77].

In a 3-year retrospective analysis of 507 low- and high-risk histology cases undergoing SLN mapping, a gradual decrease in the number of completion lymphadenectomy procedures was identified along with a decrease in the average number of lymph nodes removed [78]. There was no difference in the annual number of cases identified with lymph node metastasis (Y1, 7.0%; Y2, 7.9%; Y3, 7.5%; $p = 1.0$), despite the decreasing proportion of lymphadenectomy cases (Y1, 65.0%; Y2, 35.0%; Y3, 23.0%; $p < 0.001$). The authors suggested that the SLN algorithm may reduce the need for standard lymphadenectomy and did not appear to adversely affect the detection of stage IIIC disease. It has also been recognized that approximately 5% of SLNs are located in areas not routinely dissected with pelvic lymphadenectomies, such as presacral and deep internal iliac lymph nodes [65].

More recently, staging results from patients undergoing lymphadenectomy ($N = 661$) versus SLN mapping plus lymphadenectomy ($N = 119$) were retrospectively compared [64]. Despite equivalency in demographics and uterine tumor pathology risk factors for metastasis, the SLN group had more lymph node metastasis (30.3% vs. 14.7%, $p < 0.001$), more stage IIIC disease (30.2% vs. 14.5%, $p < 0.001$), more GOG high-risk cases (32.8% vs. 21.8%, $p = 0.013$), and received more adjuvant therapy (28.6% vs. 16.3%, $p < 0.01$). The SLN was the only

metastasis in 18 (50%) of mapped cases with positive nodes, and the false-negative rate was 2.8%. Performance of SLN mapping with staging lymphadenectomy increased the detection of lymph node metastasis (OR 3.29, 1.87–5.82; $p < 0.001$) [77].

6.7 SLN Mapping Surgical Algorithm

The NCCN currently recommends an algorithm that focuses on resecting all suspicious nodes, performing a full lymphadenectomy on any side that does not map, and ultrastaging of SLNs [8]. Guidelines highlight on completing a side-specific lymphadenectomy on any hemipelvis that fails to map due to an increased risk of metastasis in the absence of failed mapping. Suggested reasons for mapping failure include lymphatic obstruction by tumor in cases with clinically positive nodes [33], obesity, and use of blue dye only [60].

Barlin et al. described a reduction in the false-negative rate in patients mapped with blue dye from 15% to 2% when an SLN algorithm that included side-specific lymphadenectomy for mapping failure was followed [33]. Rajanbabu et al. looked into the performance of sentinel lymph node mapping alone and sentinel lymph node mapping algorithm in various endometrial cancer risk groups using ICG dye [79]. The authors reported the high concordance rate in the performance of SLN mapping alone and the surgical algorithm in low- and intermediate-risk endometrial cancer with sensitivity and NPV of 100%. In high-risk endometrial cancer, the SLN mapping alone had the sensitivity of only 57.1%, and false-negative rate (FNR) of 42.9% in detecting lymph node metastasis. Application of surgical algorithm improved the sensitivity to 100% and FNR of 0 in high-risk groups. Hence the authors concluded that to improve the diagnostic accuracy of SLN mapping in endometrial cancer, it is essential to follow the SLN algorithm. As SLN mapping alone seems to have limitations in detecting positive nodes, especially in high-risk endometrial cancer.

Given the higher rates of lymph node metastasis, the utility of SLN mapping for patients with high-grade tumor has been evaluated separately from patients with low-grade tumors. Ducie et al. evaluated the efficacy of the SLN algorithm in detecting metastasis in patients with intermediate and high-risk endometrial cancer [80]. The authors reported that the NCCN SLN algorithm provided similar detection rates of stage IIIC endometrial cancer versus complete lymphadenectomy. In patients, with high-risk tumors, stage IIIC was diagnosed in 19.4% of patients undergoing lymphadenectomy, and 21.7% of patients undergoing SLN mapping ($p = 0.68$).

Soliman et al. [81] reported a SLN detection rate of 89% from a prospective study of high-grade or deeply invasive endometrial cancer for which SLN mapping was followed by completion pelvic and aortic lymphadenectomy. They also confirmed that SLN mapping accurately identified positive nodes when combined with a side-specific lymphadenectomy per the NCCN algorithm [82], with a false-negative rate of 4.5% [81].

6.8 Outcomes of SLN Mapping for Endometrial Cancer

The primary objective of SLN mapping in endometrial cancer is to identify the lymph nodes most at risk for metastasis in order to limit complete lymphadenectomy procedures and their associated morbidities. To assure the accuracy of staging, SLN mapping requires a high SLN detection rate, high sensitivity for detection of metastasis, and a low false-negative rate as close to zero as possible.

6.8.1 Detection Rate

Detection rate is defined as a proportion of cases where at least one SLN is identified.

How et al. published an updated meta-analysis of SLN mapping for endometrial cancer in April 2018 analyzing 48 eligible studies including 5348 women [83]. The pooled overall SLN detection rate was 87% (95% CI, 84–89%), and pooled bilateral SLN detection rate was 61% (95% CI, 56–66%). The pooled para-aortic SLN detection rate was 6% (95% CI, 3–9%). The use of ICG and cervical injection was associated with an increased overall and bilateral SLN detection rate.

Meta-analysis from John Hopkins, analyzing 55 eligible studies including 4915 women, the pooled overall SLN detection rate was 81% (95% CI, 77–84) with 51% (95% CI, 45–54) bilateral detection rate, and 66% (95% CI, 62–70) side-specific detection rate [84]. The pooled para-aortic SLN detection rate was relatively high at 17% (95% CI, 11–23). The authors also reported that the cervical injection and the indocyanine green dye usage were associated with a significantly high ($p < 0.05$) SLN detection rate. There was no association seen between the SLN detection rate and histology, tumor grade, average body mass index, surgical approach, and study size.

6.8.2 Diagnostic Accuracy

Diagnostic accuracy of any test rests on its false-negative rate (FNR). FNR is defined as detecting lymph node metastasis in the completion lymphadenectomy specimen when an SLN was identified and was found to be tumor free (a false-negative case means that one or more metastatic nodes would have been undetected if a concomitant lymphadenectomy was not performed). Obviously, this rate should be as close to zero as possible.

With the initial studies of SLN mapping by Abu-Rustum et al., using the intracervical injection of blue dye, a low false-negative rate was demonstrated [85]. The SENTI-ENDO trial on sentinel node biopsy in early-stage endometrial cancer, using the cervical dual injection (patent blue with technetium) reported the NPV of 97% and sensitivity of 84%, considering the patient as the unit of analysis. The 16% of false-negative cases had type 2 endometrial cancer. Hence the author concluded utility of SLN mapping in low- or intermediate-risk endometrial cancer [49].

Recently completed prospective multi-institutional FIRES trial evaluated the diagnostic accuracy of SLN mapping in endometrial cancer using intracervical injection of ICG dye [41]. The negative predictive value and sensitivity of SLN mapping were 99.6% (95% CI, 97.9–100) and 97.2% (95% CI 85–100), respectively. Fifty-four percent of all nodal metastasis were detected with ultrastaging in the study. However, the trial was inconclusive with regard to the accuracy of SLN mapping in high-risk groups because of the inclusion of a small proportion of patients with high-grade tumors (26%).

The John Hopkins meta-analysis reported the pooled sensitivity and negative predictive value of SLN detection of metastatic disease of 96% (95% CI, 93–98) and 99.7%, respectively. Interestingly, the meta-analysis did not identify a significant difference in the sensitivity of SLN mapping with ultrastaging [84].

Similarly in the Canadian meta-analysis, How et al. reported a very high degree of diagnostic accuracy of SLN mapping in detecting endometrial cancer metastasis with pooled sensitivity of 94% (95% CI 91–96) and NPV of 100% (95% CI 99–100). The sensitivity of SLN biopsy was not affected with the usage of cytokeratin in ultrastaging. The authors also reported no difference in sensitivity among studies evaluating high-risk patients (94%, 95% CI 86–98%) compared to the mixed-risk patients (93%, 95% CI 81–99). Pooled NPV estimates were the same for both these groups (99%). Hence the authors concluded that the SLN mapping is a feasible and accurate alternative to systematic lymphadenectomy that may potentially be a more appropriate option even for high-risk endometrial cancer [83].

6.9 Impact of SLN Mapping on Adjuvant Treatment

Due to increased sensitivity to detect metastatic disease in the LNs, several studies have reported changes in their postoperative management. Holloway et al. compared 119 patients who underwent SLN mapping with completion lymphadenectomy to 661 patients who only underwent lymphadenectomy [77]. In their study, SLN mapping had a significant effect on the detection of metastatic disease (Aor = 3.29, 95% CI 1.87–5.82; $p < 0.001$) with the SLN being the only metastatic disease in 18 (50%) of mapped cases with positive nodes. Furthermore, the SLN group was more likely to receive postoperative adjuvant chemotherapy and radiation therapy (28.6% vs 16.3%, $p < 0.003$).

In a French multicenter trial, Raimond et al. found that successfully mapped SLNs were threefold more likely to contain metastatic disease than LNs following systematic lymphadenectomy, resulting in a higher rate of external beam radiation therapy given to SLN group ($p < 0.001$) [58]. Additionally, in the long-term studies of the SENTI-ENDO trial, Darai et al. reported that ultrastaging allowed a change in adjuvant therapy where 37.5% of patients with metastases detected by the SLN were able to receive more chemotherapy and radiation [49].

6.10 Impact of SLN Mapping on Oncologic Outcomes

Currently, few clinical studies have compared the recurrence patterns and survival in women with endometrial cancer staged by the SLN algorithm versus pelvic and aortic lymphadenectomy. All have demonstrated at least non-inferiority to standard or selective lymphadenectomy regardless of histology [58, 86–88]. Even in "best case" scenarios, not all recurrences can be prevented with staging lymphadenectomy (SLN or complete), but sidewall recurrences in the nodal basins should be minimized if there is any value in the identification of appropriate lymph nodes and their treatment.

How et al. reported a 68% reduction of pelvic sidewall recurrences in patients staged with SLN biopsies followed by completion lymphadenectomy compared to routine lymphadenectomy procedures (HR 0.32, $p = 0.07$) [88]. They attributed this to the detection of SLNs in unusual locations. In a follow-up study, the same authors have reported the detection rate of 14.6% metastatic LNs in atypical locations (including presacral, parametrial, and internal iliac vein nodes) that are not routinely sampled in complete lymphadenectomy [89].

In a comparison of complete lymphadenectomy at the Mayo Clinic (Rochester, MN) to the SLN algorithm at Memorial Sloan Kettering Cancer Center (New York, NY), pelvic node metastasis was identified in 2.6% and 5.1% of patients, respectively ($p = 0.03$), and aortic node metastases in 1.0% and 0.8%, respectively ($p = 0.75$). Myometrial invasion was absent in 29% and 57% of tumors, respectively. Despite some differences in patient characteristics and adjuvant therapy, the 3-year disease-free survival rates were not different 96.8% [95% CI, 95.2–98.5] and 94.9% [95% CI, 92.4–97.5], respectively. These data support the use of the SLN algorithm for staging patients with endometrioid adenocarcinoma with less than 50% myometrial invasion [90].

Similarly, in an Italian retrospective analysis, selective lymphadenectomy based on intraoperative frozen section strategy at Rome centre and SLN mapping strategy at Monza centre were compared to look into the impact on survival in the all-risk group early-stage endometrial cancer. Positive pelvic LNs were 16.7% and 7.3% in SLN and LD group, respectively ($p = 0.002$). Despite some differences in adjuvant treatment, brachytherapy with/without EBRT were administered only in Rome group, the 3-year comparison of disease-free survival curves showed no significant differences between centers and strategies adopted with an HR of 0,87 (95% CI, 0.63–2.16, $p = 0.475$). The same authors have found no difference in the 3-year disease-free and overall survival in the high-intermediate (121 patients) and high-risk (145 cases) ESMO/ESGO/ESTRO groups when comparing the SLN algorithm strategy with selective lymphadenectomy [91].

Similar survival comparisons have been reported for patients with carcinosarcoma managed with the SLN algorithm versus lymphadenectomy [86]. In a study, of 136 patients with uterine carcinosarcoma, 48 had surgical staging with SLN mapping and 88 had routine lymphadenectomy consisting of pelvic and/or para-aortic lymph node dissection. The median number of lymph nodes removed was 8 and 20,

respectively ($p \leq 0.001$); however, the median number of positive nodes was similar between the groups ($p = 0.2$). There was no difference in median progression-free survival between the SLN and lymphadenectomy groups (23 vs. 23.2 months, respectively; $p = 0.7$).

High-risk uterine papillary serous carcinoma has also been evaluated in a cohort of 248 patients (153 using the SLN algorithm, 95 with routine lymphadenectomy) [87]. Median nodes removed in the SLN versus lymphadenectomy groups were 12 (range, 1–50) and 21 (range, 1–75), respectively ($p < 0.001$). There were no differences in adjuvant therapy or 2-year progression-free survival (77% vs. 71%, respectively, $p = 0.3$) [88]. These data suggest the possible safety of the NCCN SLN algorithm in the surgical staging of high-risk histology, however, larger multi-institutional studies with long-term follow up needs to be performed before lymphadenectomy is abandoned in high-grade disease.

6.11 Controversial Issues

While the current information from SLN mapping studies in endometrial cancer appears quite promising, there are many controversies. The accuracy of the technique across practitioners, appropriate patient selection, optimal treatment algorithm to differentially manage high- and low-grade patients, the role of para-aortic dissection, and the clinical significance of ITC node metastasis require further research.

6.11.1 Role of Para-Aortic LN Dissection with SLN Mapping

Use of the SLN surgical algorithm may be associated with failure to diagnose isolated positive para-aortic disease. The risk for isolated para-aortic nodal metastases is approximately 3% [92, 93]. Failure to identify para-aortic metastases potentially results in failure to prescribe appropriate adjuvant therapy. This issue is particularly relevant with SLN detection using cervical injection of dyes, because of the lower rates of para-aortic SLN detection compared to fundal or intra-tumoral injections [38, 71].

The publication from MSKCC has demonstrated a very low incidence of isolated para-aortic metastases in the absence of pelvic nodal metastases, even in high-grade lesion (1%) [94]. This was further supported by a study from Chiang et al. who pooled the results from 18 studies from 1983 to 2011, and found a 1.5% cumulative rate of isolated para-aortic nodal metastasis [95].

In the FIRES trial, completion para-aortic dissection was performed in 58% of all patients and 74% of patients with high-grade cancers. No cases of missed isolated para-aortic nodal metastases were observed among patients who mapped at least one SLN and underwent para-aortic lymphadnectomy, however not all patients underwent an infra-renal dissection. Isolated para-aortic metastases were correctly identified in the para-aortic sentinel nodes following cervical injection in 3 (<1%) cases [41].

In order to overcome these challenges with SLN mapping, SGO consensus statement has recommended the consideration of following strategies. Preoperative imaging in patients at high risk for lymph node metastases (high-grade tumors) to identify suspicious lymph nodes in the para-aortic region that should be surgically evaluated regardless of mapping results. In addition, frozen section analysis to identify invasion greater than 50% identifies patients at high risk for para-aortic metastasis, as well as positive pelvic nodes. Intraoperatively, close inspection of para-aortic region for the identification of true SLN's (as opposed to secondary echelon nodes) particularly among those patients who appear to have failed to map a pelvic SLN. Among patients at higher risk for occult para-aortic disease (high-grade histology, deeply invasive uterine tumors, and positive pelvic nodes) surgeons can elect to perform para-aortic lymphadenectomy, and rely on the SLN algorithm exclusively for pelvic nodal evaluation.

6.11.2 Low-Volume Metastasis

SLN mapping allows ultrastaging, resulting in the detection of micrometastasis (MM) and isolated tumor cells (ITCs). Currently, the prognostic significance of MM and ITCs is not well defined [96, 97]. Current NCCN breast cancer guidelines state that routine IHC is not recommended, and that treatment decisions should be based on H&E results. However, both the biology and the natural history of breast and endometrial cancers are quite different, and the application of breast cancer guidelines to endometrial cancer is untested. For endometrial cancer, low-volume metastases found with ultrastaging make up approximately half of the lymph node metastases identified through SLN assessments [49, 57–59, 63, 77]. Occult (IHC positive) lymph node metastases in SLNs or non-SLNs are associated with high-risk uterine features such as lymph-vascular space invasion and deep myometrial invasion, and are associated with a higher rate of recurrence [98, 99]. Recurrence rates for patients with SLN micrometastases who were treated with adjuvant therapy approximate those of patients without metastases, but it is uncertain what impact adjuvant therapy has on these patients' outcomes [100]. The presence of ITCs or micrometastases may represent a prognostic biomarker in terms of survival outcomes, but it is still unknown whether the presence of ITCs should be used as a predictive biomarker, independent of other histopathology risk factors for metastasis or recurrence.

6.11.3 Proficiency for the SLN Technique

At present there is a lack of learning curve data for SLN technique in endometrial cancer. Investigators from MSKCC has described a learning curve with an increase in SLN detection from 77% to 94% ($p = 0.03$) following a 30-case experience [76]. Based on the American Society of Clinical Oncology (ASCO) guidelines for application of the technique in breast cancer [101], the SGO consensus

has recommended the completion of at least 20 SLN procedures with concomitant completion lymphadenectomy by a surgeon prior to adopting an SLN algorithm.

6.12 Summary

Based on the evidence in a large amount of literature, the Society of Gynecology Oncology has published a review with consensus recommendation emphasizing the fact that SLN detection with cervical injection of a tracer is shown to be accurate for the detection of pelvic lymph node metastasis, with a false-negative rate <5% when the NCCN surgical SLN algorithm is closely followed. When available, ICG dye with infrared imaging is preferable because of technical ease, high success, and reliability. Moreover, the SLN mapping increases the overall detection of nodal metastasis when compared to routine systematic lymphadenectomy. The NCCN SLN algorithm appropriately stages the patients with low-grade endometrioid adenocarcinoma. Incorporating the NCCN SLN mapping algorithm into the staging of high-grade endometrial cancer (grade 3 endometrioid, serous, clear cell, or carcinosarcoma) seems to be feasible, with encouraging early results, but more data is required on the safety and efficacy of SLN biopsies alone for strong recommendations [102].

References

1. Holloway RW, Abu-Rustam NR, Backes FJ, Boggess JF, Gotlieb WH, Jeffrey Lowery W, et al. Sentinel lymph node mapping and staging in endometrial cancer: a Society of Gynecologic Oncology literature review with consensus recommendation. Gynecol Oncol. 2017 August;146(2):405–15.
2. Shepherd JH. Revised FIGO staging for gynaecological cancer. Br J Obstet Gynaecol. 1989;96:889–92.
3. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Obstet Gynaecol. 2009;105:103–4.
4. Creasmen WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread pattern of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987;60(8 Suppl):2035–41.
5. Orr JW, Holloway RW, Orr PF, Holimon JL. Surgical staging of uterine cancer: an analysis of perioperative morbidity. Gynecol Oncol. 1991;42:209–16.
6. Creasmen WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. J Epidemiol Biostat. 2001;6:47–86.
7. Zivanovic O, Khoury-Collado F, Abu-Rustam NR, Germignani ML. Sentinel lymph node biopsy in the management of vulvar carcinoma, cervical carcinoma, and endometrial cancer. Oncologist. 2009;14:695–705.
8. National Comprehensive Cancer Network. Uterine neoplasms (Version 2.2018). 2018. Available from http://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf
9. Abu-Rustam NR, Khory-Collado F, Pandit-Taskar N, et al. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? Gynecol Oncol. 2009;113:163–9.
10. Abu-Rustam NR. Sentinel lymph node mapping for endometrial cancer: a modern approach to surgical staging. JNCCN. 2014;12(2):288–97.

11. Colombo N, Creutzberg C, Amant F, et al. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016;27:16–41.
12. Press JZ, Gotlieb WH. Controversies in the treatment of early stage endometrial cancer. Obstet Gynecol Int. 2012;2012:578490.
13. Beesley VL, Rowlands IJ, Hayes SC, Janda M, O' Rourke P, Marquart L, et al. Incidence, risk factors and estimates of a woman's risk of developing secondary lower limb lymphedema and lymphedema-specific supportive care needs in a women treated for endometrial cancer. Gynecol Oncol. 2015;136:87–93.
14. Zikan M, Fischerova D, Pinkavova I, Slama J, Weinberger V, Dusek L, et al. A prospective study examining the incidence of asymptomatic and symptomatic lymphoceles following lymphadenectomy in patients with gynaecological cancer. Gynecol Oncol. 2015;137:291–8.
15. Abu-Rustam NR, Alektiar K, Iasonos A, et al. The incidence of symptomatic lower-extremity lymphedema following treatment of uterine corpus malignancies: a 12-year experience at memorial Sloan-Kettering cancer Centre. Gynecol Oncol. 2006;103:714–8.
16. Panici PB, Basile S, Maneschi F, et al. Systematic pelvic lymphadenectomy in early-stage endometrial cancer: a randomized clinical trial. J Natl Cancer Inst. 2008;100:1707–16.
17. ASTEC study group, Kitchener H, Swart AM, Qian Q, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomized study. Lancet. 2009;373:125–36.
18. Todo Y, Kato H, Kaneuchi M, et al. Survival effect of Para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective analysis. Lancet. 2010;375:1165–72.
19. Frumovitz M, Slomovitz BM, Singh DK, Broaddus RR, Abrams J, Sun CC, et al. Frozen section analysis as predictors of lymphatic spread in patients with early-stage uterine cancer. J Am Coll Surg. 2004;199:388–93.
20. Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol. 2008;109:11–8.
21. Case AS, Rocconi RP, Straughn JM, Conner M, Novak L, Wang W, et al. A prospective blinded evaluation of the accuracy of frozen section for the surgical management of endometrial cancer. Obstet Gynecol. 2006;108:1375–9.
22. Kumar S, Bandyopadhyay S, Semaan A, Shah JP, Mahdi H, Morris R, et al. The role of frozen section in surgical staging of low risk endometrial cancer. PLoS One. 2011;6:e21912.
23. Altman AD, Ferguson SE, Atenafu EG, Kobel M, McAlpine JN, Panzarella T, et al. Canadian high risk endometrial cancer (CHREC) consortium: analyzing the clinical behavior of high risk endometrial cancers. Gynecol Oncol. 2015;139:268–74.
24. Kumar S, Medeiros F, Dowdy SC, Keeney GL, Bakkum-Gamez JN, Podratz KC, et al. A prospective assessment of the reliability of frozen section to direct intraoperative decision making in endometrial cancer. Gynecol Oncol. 2012;127:525–31.
25. Stephan JM, Hansen J, Samuelson M, McDonald M, Chin Y, Bender D, et al. Intra-operative frozen section results reliably predict final pathology in endometrial cancer. Gynecol Oncol. 2014;133:499–505.
26. Cabanas RM. An approach for the treatment of penile carcinoma. Cancer. 1977;39:456–66.
27. Morton DL, Wen DR, Wong JH, Economou JS, Cagle LA, Storm FK, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg. 1992;127:392–9.
28. Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, et al. Sentinel lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11:927–33.
29. Oonk MH, van Hemel BM, Hollema H, de Hullu JA, Ansink AC, Vergote I, et al. Size of sentinel-node metastasis and chances of non-sentinel-node involvement and survival in early stage vulvar cancer: results from GROINSS-V, a multicentre observational study. Lancet Oncol. 2010;11:646–52.

30. Burke TW, Levenback C, Tornos C, Morris M, Wharton JT, Gerhenson DM. Intraabdominal lymphatic mapping to direct selective pelvic and par-aortic lymphadenectomy in women with high-risk endometrial cancer: results of a pilot study. Gynecol Oncol. 1996;62:169–73.
31. National Comprehensive Cancer Network. Vulvar cancer (Version 1.2019). 2018. Available from: http://www.nccn.org/professionals/physician_gls/pdf/vulvar.pdf
32. National Comprehensive Cancer Network. Cervical cancer (Version 1.2019). 2018. Available from: http://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf
33. Barlin JN, Khoury-Collado F, Kim CH, Leitao MM, Chi DS, Sonodo Y, et al. 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.
34. Sinno AK, Fader AN, Tanner EJ. Single site robotic sentinel lymph node biopsy and hysterectomy in endometrial cancer. Gynecol Oncol. 2015;137(1):190.
35. Sinno AK, Fader AN, Roche KL, Giuntoli RL II, Tanner EJ. A comparison of colorimetric versus fluorometric sentinel lymph node mapping during robotic surgery for endometrial cancer. Gynecol Oncol. 2014;134(2):281–6.
36. Torne A, Pahisa J, Vidal-Sicart S, Martinez-Roman S, Paredes P, Puerto B, et al. Transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR): a new method for sentinel lymph node detection in endometrial cancer. Gynecol Oncol. 2013;128(1):88–94.
37. Solima E, Martinelli F, Ditto A, Maccauro M, Carcangiu M, Mariani L, et al. Diagnostic accuracy of sentinel node in endometrial cancer by using hysteroscopic injection of radiolabeled tracer. Gynecol Oncol. 2012;126(3):419–23.
38. Niikura H, Kaiho-Sakuma M, Tokunaga H, Toyoshima M, Utsunomiya H, Nagase S, et al. Tracer injection sites and combinations for sentinel lymph node detection in patients with endometrial cancer. Gynecol Oncol. 2013;131:299–303.
39. Rossi EC, Jackson A, Ivanova A, Boggess JF. Detection of sentinel nodes for endometrial cancer with robotic assisted fluorescence imaging: cervical versus hysteroscopic injection. Int J Gynecol Cancer. 2013;23:1704–11.
40. Holloway RW, Ahmad S, Kendrick JE, Bigsby GE, Brudie LA, Ghurani GB, et al. A prospective cohort study comparing colorimetric and fluorescent imaging for sentinel lymph node mapping in endometrial cancer. Ann Surg Oncol. 2017;24(7):1972–9. https://doi.org/10.1245/s10434-017-5825-3.
41. Rossi EC, Kowalski LD, Scalici J, Cantrell L, Schuler K, Hanna RK, et al. A comparison of sentinel lymph node biopsy to lymphadenectomy for endometrial cancer staging (FIRES trial): a multicentre, prospective, cohort study. Lancet Oncol. 2017;18:384–92.
42. Kang S, Yoo HJ, Hwang JH, Lim M-C, Seo S-S, Park S-Y. Sentinel lymph node biopsy in endometrial cancer: meta-analysis of 26 studies. Gynecol Oncol. 2012;126(3):419–23.
43. Kushner DM, Connor JP, Wilson MA, Hafez GR, Chappell RJ, Stewart SL, et al. Laparoscopic sentinel lymph node mapping for cervix cancer - a detailed evaluation and time analysis. Gynecol Oncol. 2007;106:507–12.
44. Albo D, Wayne JD, Hunt KK, Rahlfs TF, Singletary SE, Ames FC, et al. Anaphylactic reactions to isosulfan blue dye during sentinel lymph node biopsy for breast cancer. Am J Surg. 2001;182:393–8.
45. Blessing WD, Stolier AJ, Teng SC, Bolton JS, Fuhrman GM. A comparison of methylene blue and lymphazurin in breast cancer sentinel node mapping. Am J Surg. 2002;184:341–5.
46. Levenback C, Ali S, Coleman RL, Gold MA, Fowler JM, Judson PL, et al. Lymphatic mapping and sentinel lymph node biopsy in women with squamous cell carcinoma of the vulva: a gynecologic oncology group study. J Clin Oncol. 2012;30:3786–91.
47. Veronesi U, Paganelli G, Viale G, Luini A, Zurrida S, Galimberti V, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med. 2003;349:546–53.
48. Gipponi M, Di Somma C, Peressini A, Solari N, Gliori S, Nicolo G, et al. Sentinel lymph node biopsy in patients with stage I/II melanoma: clinical experience and literature review. J Surg Oncol. 2004;85:133–40.
49. Ballester M, Dubernard G, Lecuru F, Heitz D, Mathevet P, Marret H, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol. 2011;12:469–76.

50. Perissinotti A, Paredes P, Vidal-Sicart S, Torne A, Albela S, Navales I, et al. Use of SPECT/CT for improved sentinel lymph node localization in endometrial cancer. Gynecol Oncol. 2013;129:42–8.
51. Jewell EL, Huang JJ, Abu-Rustum NR, Gardner GJ, Brown CL, Sonoda Y, et al. 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;133:274–7.
52. Rossi EC, Ivanova A, Boggess JF. Robotically assisted fluorescence-guided lymph node mapping with ICG for gynecologic malignancies: a feasibility study. Gynecol Oncol. 2012;124:78–82.
53. Papadia A, Buda A, Gasparri ML, Martino GD, Bussi B, Verri D, et al. The impact of different doses of indocyanine green on the sentinel lymph-node mapping in early stage endometrial cancer. J Can Res & Clin Oncol. 2018;144:2187–91.
54. Frumovitz M, Plante M, Lee PS, Sandadi S, Lilija JF, Escobar PF, et al. Near-infrared fluorescence for detection of sentinel lymph node in women with cervical and uterine cancers (FILM): a randomised, phase 3, multicentre, non-inferiority trial. Lancet Oncol. 2018;19:1394–403.
55. Cochran AJ. Prediction of outcome for patients with cutaneous melanoma. Pigment Cell Res. 1997;10:162–7.
56. Compton CC, Byrd DR, Garcia-Aguilar J, Kurtzman SH, Olawaiye A, Washington MK. AJCC cancer staging atlas. New York, NY: Springer; 2012.
57. Kim CH, Soslow RA, Park KJ, Barber EL, Khoury-Collado F, Barlin JN, et al. Pathologic ultrastaging improves micrometastasis detection in sentinel lymph nodes during endometrial cancer staging. Int J Gynecol Cancer. 2013;23(5):964–70.
58. Raimond E, Ballester M, Hudry D, Bendifallah S, Darai E, Graesslin O, et al. Impact of sentinel lymph node biopsy on the therapeutic management of early stage endometrial cancer: results of a retrospective multicentre study. Gynecol Oncol. 2014;133(3):506–11.
59. Touhami O, Trinh XB, Gregoire J, Sebastianelli A, Renaud MC, Grondin K, et al. Predictors of non-sentinel lymph node (non-SLN) metastasis in patients with sentinel lymph node (SLN) metastasis in endometrial cancer. Gynecol Oncol. 2015;138:41–5.
60. Tanner EJ, Sinno AK, Stone RL, Levinson KL, Long KC, Fader AN. Factors associated with successful bilateral sentinel lymph node mapping in endometrial cancer. Gynecol Oncol. 2015;138:542–7.
61. Bats AS, Mathevet P, Buenerd A, Orliaguet I, Mery E, Zerdoud S, et al. The sentinel node technique detects unexpected drainage pathways and allows nodal ultrastaging in early cervical cancer: insights from the multicenter prospective SENTICOL study. Ann Surg Oncol. 2013;20:413–22.
62. Delaloye JF, Pampallona S, Chardonnens E, Fiche M, Lehr HA, De Grandi P, et al. Intraoperative lymphatic mapping and sentinel node biopsy using hysteroscopy in patients with endometrial cancer. Gynecol Oncol. 2007;106:89–93.
63. Desai PH, Hughes P, Tobias DH, Tchabo N, Heller PB, Dise C, et al. Accuracy of robotic sentinel lymph node detection (RSLND) for patients with endometrial cancer (EC). Gynecol Oncol. 2014;135:196–200.
64. Favero G, Pfiffer T, Ribeiro A, Carvalho JP, Baracat EC, Mechsner S, et al. Laparoscopic sentinel lymph node detection after hysteroscopic injection of technetium-99 in patients with endometrial cancer. Int J Gynecol Cancer. 2015;25:423–30.
65. How J, Gotlieb WH, Press JZ, Abitbol J, Pelmus M, Ferenczy A, et al. Comparing indocyanine green, technetium, and blue dye for sentinel lymph node mapping in endometrial cancer. Gynecol Oncol. 2015;137:436–42.
66. How J, Lau S, Press J, Ferenczy A, Pelmus M, Stern J, et al. Accuracy of sentinel lymph node detection following intra-operative cervical injection for endometrial cancer: a prospective study. Gynecol Oncol. 2012;127:332–7.
67. Lopes LA, Nicolau SM, Baracat FF, Baracat EC, Goncalves WJ, Santos HV, et al. Sentinel lymph node in endometrial cancer. Int J Gynecol Cancer. 2007;17:1113–7.
68. Lopez-De la Manzanara Cano C, Cordero Garcia JM, Martin-Francisco C, Pascual-Ramirez J, Parra CP, Cespedes Casas C. Sentinel lymph node detection using 99mTc combined with

methylene blue cervical injection for endometrial cancer surgical management: a prospective study. Int J Gynecol Cancer. 2014;24:1048–53.
69. Mais V, Peiretti M, Gargiulo T, Parodo G, Cirronis MG, Melis GB. Intraoperative sentinel lymph node detection by vital dye through laparoscopy or laparotomy in early endometrial cancer. J Surg Oncol. 2010;101:408–12.
70. Plante M, Touhami O, Trinh XB, Renaud MC, Sebastianelli A, Grondin K, et al. Sentinel node mapping with indocyanine green and endoscopic near-infrared fluorescence imaging in endometrial cancer. A pilot study and review of the literature. Gynecol Oncol. 2015;137:443–7.
71. Robova H, Charvat M, Strnad P, Hrehorcak M, Taborska K, Skapa P, et al. Lymphatic mapping in endometrial cancer: comparison of hysteroscopic and subserosal injection and the distribution of sentinel lymph nodes. Int J Gynecol Cancer. 2009;19:391–4.
72. Sawicki S, Lass P, Wydra D. Sentinel lymph node biopsy in endometrial cancer: comparison of 2 detection methods. Int J Gynecol Cancer. 2015;25:1044–50.
73. Vidal F, Leguevaque P, Motton S, Delotte J, Ferron G, Querleu D, et al. Evaluation of the sentinel lymph node algorithm with blue dye labeling for early-stage endometrial cancer in a multicentric setting. Int J Gynecol Cancer. 2013;23:1237–43.
74. Li B, Li XG, Wu LY, Zhang WH, Li SM, Min C. A pilot study of sentinel lymph node identification in patients with endometrial cancer. Bull Cancer. 2007;94:E1–4.
75. Mucke J, Klapdor R, Schneider M, Langer F, Gratz KF, Hillemanns P. Isthmocervical labelling and SPECT/CT for optimized sentinel detection in endometrial cancer: technique, experience and results. Gynecol Oncol. 2014;134:287–92.
76. Khoury-Collado F, Glaser GE, Zivanovic O, Sonoda Y, Levine DA, Chi DS, et al. Improving sentinel lymph node detection rates in endometrial cancer: how many cases are needed? Gynecol Oncol. 2009;115:453–5.
77. Holloway RW, Gupta S, Stavitzski NM, Zhu X, Takimoto EL, Gubbi A, et al. Sentinel lymph node mapping with staging lymphadenectomy for patients with endometrial cancer increases the detection of metastasis. Gynecol Oncol. 2016;141:206–10.
78. Leitao MM, Khoury-Collado F, Gardner G, Sonoda Y, Brown CL, Alektiar KM, et al. 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;129:38–41.
79. Rajanbabu A, Agarwal R. A prospective evaluation of the sentinel node mapping algorithm in endometrial cancer and correlation of its performance against endometrial cancer risk subtypes. Eur J Obstet Gynecol Reprod Biol. 2018;224:77–80.
80. Ducie JA, Eriksson AGZ, Ali N, McGree ME, Weaver AL, Bogani G, et al. Comparison of a sentinel lymph node mapping algorithm and comprehensive lymphadenectomy in the detection of stage IIIC endometrial carcinoma at higher risk for nodal disease. Gynecol Oncol. 2017;147:541–8.
81. Soliman P, Westin S, Dioun S, Sun C, Euscher E, Munsell M, et al. Sentinel lymph node mapping accurately identifies positive nodes in women with high risk endometrial cancer: a prospective validation trial. Int J Gynecol Cancer. 2016;26(Suppl.3):68.
82. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms, Version 1.2017. 2016.
83. How J, Farrell PO, Amajoud Z, Lau S, Salvador S, How M, et al. Sentinel lymph node mapping in endometrial cancer: a systematic review and meta-analysis. Minerva Ginecol. 2018;70(2):194–214.
84. Bodurtha SAJ, Fader AN, Tanner EJ. Sentinel lymph node assessment in endometrial cancer: a systematic review and meta-analysis. Am J Obstet Gynecol. 2017;216(5):459–76. e10
85. Abu-Rustum NR, Khoury-Collado F, Pandit-Taskar N, Soslow RA, Dao F, Sonoda Y, et al. Sentinel lymph node mapping for grade 1 endometrial cancer: is it the answer to the surgical staging dilemma? Gynecol. Oncologia. 2009;113:163–9.
86. Schiavone M, Scelzo C, Straight C, Zhou Q, Letiao M, Alektiar K, et al. Survival in patients with serous uterine carcinoma undergoing sentinel lymph node mapping. Int J Gynecol Cancer. 2016;26:74–5.

87. Schiavone M, Scelzo C, Straight C, Zhou Q, Alektiar K, Makker V, et al. Survival of patients with serous uterine carcinoma undergoing sentinel lymph node mapping. Ann Surg Oncol. 2017;24:1965–71.
88. How J, Gauthier C, Abitbol J, Lau S, Salvador S, Gotlieb R, et al. Impact of sentinel lymph node mapping on recurrence patterns in endometrial cancer. Gynecol Oncol. 2017;144:503–9.
89. How J, Boldeanu I, Lau S, Salvador S, How E, Gotlieb R, et al. Unexpected locations of sentinel lymph nodes in endometrial cancer. Gynecol Oncol. 2017;147(1):18–23.
90. Zahl Eriksson AG, Ducie J, Ali N, McGree ME, Weaver AL, Bogani G, et al. Comparison of a sentinel lymph node and a selective lymphadenectomy algorithm in patients with endometrioid endometrial carcinoma and limited myometrial invasion. Gynecol Oncol. 2016;140:394–9.
91. Buda A, Restaino S, Martino GD, Ponti ED, Monterossi G, Dinoi G, et al. The impact of the type of nodal assessment on prognosis in patients with high-intermediate and high-risk ESMO/ESGO/ESTRO group endometrial cancer. A multicentre Italian study. Eur J Surg Oncol. 2018;44:1562–7.
92. Khoury-Collado F, Murray MP, Hensley ML, Sonoda Y, Alektiar KM, Levine DA, et al. Sentinel lymph node mapping for endometrial cancer improves the detection of metastatic disease to regional lymph nodes. Gynecol Oncol. 2011;122:251–4.
93. Kumar S, Podratz KC, Bakkum-Gamez JN, Dowdy SC, Weaver AL, McGree ME, et al. Prospective assessment of the prevalence of pelvic, paraaortic and high paraaortic lymph node metastasis in endometrial cancer. Gynecol Oncol. 2014;132:38–43.
94. Abu-Rustam NR, Gomez JD, Alektiar KM, et al. The incidence of isolated paraaortic nodal metastasis in surgically staged endometrial cancer patients with negative pelvic lymph nodes. Gynecol Oncol. 2009;115:236–8.
95. Chiang AJ, Yu KJ, Chao KC, Teng NN. The incidence of isolated Para-aortic nodal metastasis in completely staged endometrial cancer patients. Gynecol Oncol. 2011;121:122–5.
96. Pelosi E, Arena V, Baudino B, Bello M, Giusti M, Gargiulo T, et al. Pre-operative lymphatic mapping and intraoperative sentinel lymph node detection in early stage endometrial cancer. Nucl Med Commun. 2003;24:971–5.
97. Cormier B, Rozenholc AT, Gotlieb W, Plante M, Giede C. Communities of practice Group of the Society of gynecologic oncology of Canada. Sentinel lymph node procedure in endometrial cancer: a systematic review and proposal for standardization of future research. Gynecol Oncol. 2015;138:478–85.
98. Todo Y, Suzuki Y, Azuma M, Hatanaka Y, Konno Y, Watari H, et al. Ultrastaging of paraortic lymph nodes in stage IIIC1 endometrial cancer: a preliminary report. Gynecol Oncol. 2012;127:532–7.
99. Yabushita H, Shimazu M, Yamada H, Sawaguchi K, Noguchi M, Nakanishi M, et al. Occult lymph node metastases detected by cytokeratin immunohistochemistry predict recurrence in nodenegative endometrial cancer. Gynecol Oncol. 2001;80:139–44.
100. St Clair CM, Eriksson AG, Ducie JA, Jewell EL, Alektiar KM, Hensley ML, et al. Low-volume lymph node metastasis discovered during sentinel lymph node mapping for endometrial carcinoma. Ann Surg Oncol. 2016;23:1653–9.
101. Lyman GH, Giuliano AE, Somerfield MR, Benson AB, Bodurka DC, Burstein HJ, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol. 2005;23:7703–20.
102. Naoura I, Canlorbe G, Bendifallah S, Ballester M, Darai E. Relevance of sentinel lymph node procedure for patients with high-risk endometrial cancer. Gynecol Oncol. 2015;136(1):60–4.

Minimal Invasive Surgery for Management of Endometrial Cancer

7

Sarika Gupta and Seema Singhal

7.1 Introduction

The management of endometrial cancer is predominantly surgical. The surgical management is aimed to accurately stage the disease with removal of cancer. The surgery includes careful inspection of all abdominal quadrants, pelvic washings, Type I extrafascial hysterectomy, bilateral salpingo-oophorectomy and pelvic, and para-aortic lymph node dissection. High-quality evidence has demonstrated that minimal invasive techniques in management of endometrial cancer impart patients the benefits of minimal invasive approach with comparable oncological outcomes [1, 2]. Consequently, minimal invasive surgery is endorsed by leading oncological societies as a standard of care. The Society of Gynecologic Oncologists (SGO) and the American College of Surgeons' Commission on Cancer jointly preferred the use of MIS for the treatment of stage I–III endometrial cancer in 2014 [3]. The SGO Clinical Practice Committee and the American College of Obstetricians and Gynecologists (ACOG) have also stated that "Minimally invasive surgery should be embraced as the standard surgical approach for comprehensive surgical staging in women with endometrial cancer" [4]. Similarly, the National Comprehensive Cancer Network (NCCN) guidelines also recommend that hysterectomy is justifiably performed by an MIS approach in those with apparent uterine-confined disease [5].

At the outset, embracement of minimal invasive surgery for endometrial cancer was slow, owing to fear of worse oncological outcome and longer learning curve of laparoscopic surgery. There were many apprehensions about the use of minimal

S. Gupta (✉)
Gynecologic Oncology, Indraprastha Apollo Hospital, Delhi, India

S. Singhal
Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_7

invasive surgery in endometrial cancer. The first concern with laparoscopic cancer staging was a potential risk of intra-abdominal metastases and port site metastases (PSM) linked to long periods of intra-abdominal pressure. The other risks were dissemination with pressure of uterine manipulator and the disruption of uterus while extraction from vagina. Reassuringly, several RCT's and meta-analysis have confirmed the non-inferiority of minimal access surgery in uterine cancer. The rationale behind non-inferiority of minimal invasive surgery in endometrial cancer is that most cases of endometrial cancer present in uterine-confined disease and the risk of spillage is low in the hands of a trained laparoscopic/robotic surgeon. The robot has been a key player in surgeon acceptance owing to its shorter learning curve, ergonomic convenience, and precision.

Other concern of high conversion rate to laparotomy in women with higher BMI, advanced disease, and higher age is seen to be declining with the evolution of minimal invasive surgery expertise and machinery. Further, minimal invasive surgery fares additional advantage in women with morbid obesity and women choosing sentinel node biopsy.

7.2 Outcomes of Laparoscopy

Laparoscopic staging for endometrial cancer requires advanced skills and continued practice (Fig. 7.1). Laparoscopy was first introduced in the management of endometrial cancer by Childer's et al. in 1991 [6]. They published their technique and a retrospective series of 59 women concluding that the surgical goals of cancer staging can be easily met with minimal invasive surgery [7]. Multiple subsequent retrospective studies continued to demonstrate short-term safety and advantages of

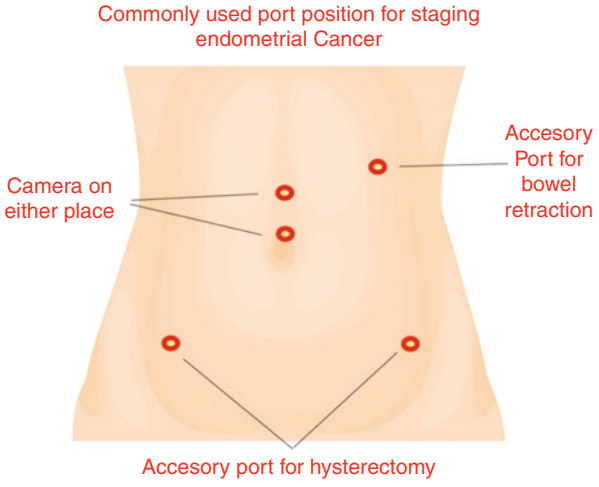


Fig. 7.1 Commonly used laparoscopic port positions for staging endometrial cancer

laparoscopy [8–10]. The concerns of cancer recurrence rates with laparoscopy were first deterred by the publication of the results of the GOG-LAP2 study [11]. This was the first-ever randomized controlled trial comparing the open vs laparoscopic staging techniques. The trial composed of 2616 women with endometrial cancer randomized to laparoscopy and laparotomy. 1696 women in laparoscopy group and 920 women in laparotomy group had similar rates of intraoperative complications, fewer grade 2–3 postoperative complications, and longer operative time (204 vs 130 min, respectively). The lymph node counts and the detection of advanced disease were similar in both the groups.

Postoperative stay longer than 2 days was significantly higher in the laparotomy group. The quality of life at 6 weeks after surgery was superior in women who underwent minimal invasive surgery. Follow-up data at 59 months reassured equivalent 5-year survival (89% in both groups) and 5-year recurrence rates (13.6% laparoscopy and 11.6% open group) [12].

Since then, eight more randomized controlled trials have assessed 3944 women for non-inferiority of laparoscopy over laparotomy [13–20].

The most recent and second largest trial is the Laparoscopic Approach to Cancer of the Endometrium (LACE) trial. It is a multinational randomized trial (n = 760) of women with stage I endometrioid EC who underwent staging with laparoscopy and laparotomy access and found no difference in disease-free survival at 4.5 years (81.6 versus 81.3%) or overall survival (mortality: 7.4 versus 6.8%), respectively.

Cochrane updated the meta-analysis of nine available RCT's in 2018 [21]. Six studies reported overall survival (OS) and recurrence-free survival (RFS) and used appropriate statistical techniques (Table 7.1). Analysis of these six studies (3993 women) found no significant difference in the risk of death between women who underwent laparoscopy and women who underwent laparotomy (HR 1.04, 95% 0.86 to 1.25; moderate certainty evidence) and five studies assessing 3710 participants found no significant difference in the risk of recurrence between the laparoscopy and laparotomy groups (HR 1.14, 95% CI 0.90 to 1.43; moderate certainty evidence) (Table 7.2). There was no significant difference in the rate of perioperative death; women requiring a blood transfusion; or bladder, ureteric, bowel, and vascular injury.

Table 7.1 Comparison of laparoscopy and laparotomy in the treatment of endometrial cancer: overall survival

Study (RCT)	Laparoscopy (N)	Laparotomy (N)	Hazard ratio (random, 95% CI)
Tozzi 2005 [20]	63	59	1.57 (0.64, 3.86)
Zullo 2009 [1]	40	38	1.38 (0.46, 4.13)
Malzoni 2009 [17]	81	78	0.55 (0.17, 1.76)
Walker 2012 [12]	920	1682	1.00 (0.81, 1.24)
Lu 2013 [16]	151	121	1.43 (0.61, 3.40)
Janda 2017 [15]	407	353	1.06 (0.64, 1.84)

Table 7.2 Comparison of laparoscopy and laparotomy in treatment of endometrial cancer (only RCT): recurrence-free survival

Study (RCT)	Laparoscopy (no. of cases)	Laparotomy (no. of cases)	Hazard ratio (random, 95% CI)
Tozzi 2005 [20]	63	59	1.75 (0.57, 5.35)
Zullo 2009 [1]	40	38	1.40 (0.51, 3.89)
Malzoni 2009 [17]	81	78	0.58 (0.22, 1.55)
Walker 2012 [12]	909	1682	1.14 (0.87, 1.50)
Janda 2017 [15]	407	353	1.19 (0.66, 2.13)

7.3 Laparoscopic Single-Site Surgery

Laparoscopic single-site surgery is a minimal invasive approach where a single 2-cm incision is given over the umbilicus and all the instruments are introduced through a single multichannel gel port. Apart from providing better cosmesis, this approach is proposed to cause lesser pain and lesser incisional hernias. The largest feasibility and perioperative outcome in endometrial cancer were published by Fagotti and colleagues in 2012 [22]. The study demonstrated that hysterectomy, bilateral salpingo-oophorectomy with pelvic and para-aortic lymphadenectomy is feasible with single-site laparoscopic surgery. The conversion rates for laparotomy and the median lymph node counts were comparable to multiport laparoscopy. Multiple feasibility studies have been published since then, however, longer learning curve and longer duration of surgery is the main drawback of this approach [23, 24]. The routine use of LESS for endometrial cancer surgery would need larger prospective trials studying the long-term safety profile.

7.4 Robotic Surgery for Endometrial Cancer

In 2005, the Food and Drug Administration (FDA) approved robotic-assisted surgery for gynecology in the United States. The robotic instruments have endowrist technology, which allows movement in 7D space, mimicking the freedom of human hand. Endowrist instruments mimic movement of a human wrist and hence mimic motion in open surgery, allowing a shorter learning curve for surgeons well versed in conventional surgery. It also imposes lesser torque to abdominal wall and results in lesser pain. Better magnification, 3D stereoscopic view, full control of surgeon over camera and three instruments, and ergonomically sound surgeon position are few of the many advantages of robotic surgery. Robotic technology overcomes many limitations of laparoscopic surgery and expands the utilization of MIS to a greater number of patients and surgeons.

The introductory series of robotic staging for endometrial cancer was reported by Reynold's et al. in 2005 [25]. Boggess et al. in 2008 compared postoperative outcomes in 322 women who underwent endometrial cancer staging by laparotomy,

laparoscopy, and robotic-assisted laparoscopy [26]. The authors reported that the lymph node yields were higher in women undergoing robotic surgery while duration of surgery, estimated blood loss, postoperative complication rates, and duration of hospital stay were shorter in robotic surgery as compared to laparoscopy and laparotomy.

Since 2009, several large retrospective studies and two small randomized control trials have compared long- and short-term follow up after open, laparoscopic, and robotic surgical approaches (Table 7.3). A large retrospective study by Wright and colleagues evaluated 1027 women with EC who underwent laparoscopic hysterectomy and 1437 who underwent robotic hysterectomy also found no difference in the rate of complications with robotic compared with laparoscopic surgery [47].

One of the two RCT comparing robotic to traditional laparoscopy for EC randomized 101 endometrial cancer patients to hysterectomy, bilateral salpingo-oophorectomy, pelvic lymphadenectomy either by robotic-assisted laparoscopic surgery or by traditional laparoscopy [48]. The median duration of surgery was significantly lower in the robotic surgery group ($n = 50$, median time 139 min) vs traditional laparoscopy ($n = 49$, median duration 170 min), $p < 0.001$. It was noted that there were five conversions to laparotomy in the laparoscopy group vs none in the robotic group ($p = 0.027$). There were no differences in the lymph node yields and duration of hospital stay in both the groups. Eight percent of women in the traditional laparoscopy group had intraoperative complications as compared to none in the robotic surgery group and 10% vs 22% women had major postoperative complications in the traditional and robotic surgery group, respectively [49].

The clinical outcomes and cost of robotic surgery in the treatment of endometrial cancer compared to the laparoscopic approach were evaluated in another recent RCT [50]. The RCT concluded that the operative outcomes were similar in 44 women randomized to robotic surgery and 45 women to laparoscopic surgery. The cost of robotic surgery was estimated to be 41% higher than traditional laparoscopy.

There is robust literature on the survival of women treated with robotic surgery. Recurrence-free intervals in 499 consecutive endometrial adenocarcinoma patients surgically staged with robotic-assisted laparoscopy were compared to endometrial cancer recurrence-free interval statistics from the Surveillance Epidemiology and End Results database from the National Cancer Institute by Kilgore et al. Among stage IA, IB, II, and III patients, overall survival was 94.2%, 85.9%, 77.4%, and 68.6%, respectively, and was similar to the overall survival of historic data operated through open approach [51]. Another study compared 350 women who underwent robotic-assisted surgical staging with 586 women who underwent open staging. The groups were comparable in terms of age, race, body mass index, and comorbid condition [52]. It was observed that robotic surgery was associated with decreased postoperative complications and readmission rates. Operative type was not an independent prognostic factor for recurrence or overall survival in a

Table 7.3 Comparison of operative outcomes of robotic staging versus laparoscopic staging

	Number of cases RAL and CL	Conversions number (%)	All complications number (%)	Blood loss (ml) (Mean ± SD)	Length of operation (Mean ± SD (minutes))	No. of nodes (Mean ± SD)	Duration of stay (days) (Mean ± SD)
Bell et al. 2008 [27]	RAL 40	–	3 (7.5)	166 ± 225.9	184 ± 41.3	17 ± 7.8	2.3 ± 1.3
	CL 30	–	8 (26.6%)	253 ± 427.7	171.1 ± 36.2	17.1 ± 7.1	2 ± 1.2
Boggess et al. 2008 [26]	RAL 103	3 (2.9)	6 (5.82)	74.5 ± 101.2	191.2 ± 36	39.2 ± 26.2	1 ± 0.2
	CL 81	4 (4.93)	11 (13.58)	145.8 ± 105.5	213.4 ± 34.7	23.1 ± 11.4	1.2 ± 0.5
Magrina et al. 2008 [28]	RAL 27	–	7 (25.9)	133.1 ± 108.5	189.6 ± 43.5	25.9 ± 6.3	1.7 ± 0.9
	CL 31	–	6 (19.35)	262.5 ± 162.5	220.4 ± 37.5	25.9 ± 7.8	2.4 ± 1.5
Gehrig et al. 2008 [29]	RAL 49	0 (0)	5 (10.20)	106.25 ± 68.75	188 ± 38	35.45 ± 16.75	3.25 ± 2
	CL 32	1 (3.12)	6 (18.75)	262.5 ± 162.5	227.5 ± 42	27.5 ± 14	1.3 ± 0.3
Veijovich et al. 2008 [30]	RAL 24	–	–	110.8 ± 72.5	295 ± 68	17.25 ± 7.5	3.25 ± 2
	CL 4	–	–	75 ± 14.4	258.8 ± 24.6	21.6 ± 9.3	1.3 ± 0.3
Seamon et al. 2009 [31]	RAL 105	13 (12.38	11 (10.47)	88 ± 60	242 ± 53	–	1 ± 7.5
	CL 76	20 (26.31))	8 (10.52)	200 ± 150	287 ± 55	–	2 ± 2
CG et al2010 [32]	RAL 103	1 (0.97)	2 (1.94)	109 ± 83.3	237 ± 57	22 ± 10.3	1.88 ± 1.6
	CL 173	9 (5.20)	6 (3.46)	187 ± 187	178 ± 58.9	23 ± 12.2	2.31 ± 2.2
Holtz et al. 2010 [33]	RAL 13	0 (0)	2 (15.38)	58.95 ± 2061	192.5 ± 38	13 ± 3.5	1.7 ± 0.6
	CL 20	2 (10)	3 (15)	105.21 ± 10.63	156.2 ± 42	8.5 ± 4.5	1.7 ± 1.2
Jung et al 2010 [34]	RAL 28	0 (0)	2 (7.14)	–	193.18 ± 6042	–	7.92 ± 3.25
	CL 25	0 (0)	2 (8)	–	165.2 ± 43.39	–	8.08 ± 1.75
Lim et al. 2010 [35]	RAL 56	1 (1.78)	8 (14.28)	89.3 ± 45	162.6 ± 53	26.7 ± 12.8	1.6 ± 0.7
	CL 56	4 (7.14)	12 (21.42)	209.1 ± 91.8	192.3 ± 55.5	45.1 ± 20.9	2.6 ± 0.9
Shah et al. 2011 [36]	RAL 45	0 (0)	3 (6.66)	58.95 ± 20.61	252.6 ± 7.3	–	1.3 ± 0.24
	CL 118	6 (5.08)	8 (6.77)	105.21 ± 10.63	186.8 ± 2.93	–	1.44 ± 0.14

Coronado et al. 2012 [37]	RAL 71	3 (4.22)	15 (21.12)	99.4 ± 75.4	189.2 ± 35.4	–	3.5 ± 3.4
	CL 84	7 (8.33)	24 (28.57)	190 ± 119.7	218.2 ± 54.3	–	4.6 ± 4
Venkat et al. 2012 [38]	RAL 27	–	–	220.4 ± 175	331.8 ± 57.5	29.8 ± 20.25	1.7 ± 0.75
	CL 27	–	–	316.7 ± 287.5	237 ± 60	29.3 ± 15.8	1.8 ± 0.75
Escobar et al. 2012 [39]	RAL 30	0 (0)	1 (3.33)	93.75 ± 43.75	196.75 ± 65.25	24.5 ± 12.5	1.95 ± 0.75
	CL 30	1 (3.33)	2 (6.06)	215.25 ± 164.75	218.25 ± 98	16.5 ± 6	2.65 ± 1.75
Turunen et al. 2013 [40]	RAL 67	–	8 (11.94)	50 ± 162.5	210 ± 66	31.4 ± 8.11	–
	CL 150	–	23 (15.33)	100 ± 195.8	120 ± 41	33.8 ± 9.38	–
Seror et al. 2014 [41]	RAL 40	–	–	–	247.82 ± 13.5	–	6.9 ± 0.3
	CL 106	–	–	–	201.28 ± 4.9	–	7.15 ± 0.35
Chiou et al. 2015 [42]	RAL 86	–	2 (2.32)	94.8 ± 78.6	155.6 ± 45.7	25.5 ± 10.7	3.1 ± 1.1
	CL 150	–	2 (1.33)	174.2 ± 229.6	178.6 ± 58.7	23.4 ± 14.2	3.7 ± 2.2
Barrie et al. 2016 [43]	RAL 745	9 (1.20)	225 (30.2)	186	149	17	1.125
	CL 688	44 (6.39)	265 (38.51)	244	165	24	1.25
Johnson et al. 2016 [44]	RAL 353	22 (6.23)	11 (3.11)	99.6 ± 109.6	125.6 ± 32.8	22.31 ± 11.01	1.35 ± 1.68
	CL 187	1 (0.5)	3 (1.60)	115.3 ± 125.8	75.8 ± 29.3	16.5 ± 9.9	1.13 ± 0.72
Maenpaa et al. 2016 [45]	RAL 50	0 (0)	18 (36)	50 ± 23.8	139 ± 27.75	–	1 ± 0.75
	CL 49	5 (10.2)	12 (24.48)	50 ± 295	170 ± 33.25	–	2 ± 1.5
Silva et al. 2018 [46]	RAL 44	1 (2.27)	8 (18.18)	162	319.5	29.5	3
	CL 45	2 (4.44)	8 (17.77)	105.5	248	34	3

RAL robotic-assisted laparoscopy, *CL* conventional laparoscopy

multivariate analysis, incorporating stage, grade, histology, operative type, and adjuvant therapy.

Interestingly, the overall survival, disease-free survival, and disease recurrence in 415 women surgically staged at two prestigious academic centers performing either robotic or laparoscopic approach were compared retrospectively [49]. 183 women underwent robotic- and 232 women underwent laparoscopic-assisted surgery. Both groups were comparable in age, body mass index, comorbid conditions, histology, surgical stage, tumor grade, total nodes retrieved, and adjuvant therapy. There were no significant differences in survival (3-year survival 93.3% and 93.6%), DFS (3-year DFS 83.3% and 88.4%), and tumor recurrence (14.8% and 12.1%) for robotic and laparoscopic groups, respectively.

The results of several comparative studies have been pooled in meta-analysis and the results of all these reviews consistently propound lesser conversions, lesser complications, lower blood loss, and shorter hospital stay with equal oncological results [2, 53, 54].

7.5 Single Port Robotics

Yet another advancement in minimal invasive surgery is single port robotics. There are several studies demonstrating the feasibility of single port robotic surgery for endometrial cancer surgery [55–57]. Sinno et al. have also demonstrated an SLN biopsy using a robotic single-site procedure [58]. However, all the reports mention a restricted range of motion, longer learning curve, and strict case selection. Probably we need better instrumentation in the single port approach to make it more user friendly.

7.6 Controversies in MIS for Management of EC

7.6.1 Obesity

Obesity is associated with endometrial cancer and such patients have high surgical morbidity. Minimal invasive techniques are less often utilized for morbidly obese patients owing to higher conversion rates in such populations. The GOG LAP2 trial demonstrated that the odds of conversion to laparotomy during laparoscopic staging increase significantly with increase in BMI (odds ratio, 1.11; 95% confidence interval 1.09–1.13). Laparoscopy to laparotomy conversion was required in 17.5% of patients with BMI of 25 kg/m^2 and in 26.5% of patients with BMI of 34–35 kg/m^2, and 57.1% of patients with BMI greater than 40 kg/m^2, respectively [11]. Although data from randomized controlled trials has demonstrated benefits of minimal invasive surgery in EC, this approach may be underutilized in patients with obesity because of limited exposure and cardiopulmonary compromise in the Trendelenburg position. Robotic platform facilitates hysterectomy and lymphadenectomy in an obese patient with better visualization, freedom of movement, and surgeon ergonomics. Leitao et al. analyzed all patients with a BMI $\geq$40 mg/m^2 who underwent

surgical staging for endometrial cancer at Memorial Sloan Kettering Cancer Center in a 9-year period. It was realized that the percentage of morbidly obese patients receiving MIS surgery increased after addition of robotic platforms in their armamentarium. The rate of conversion in laparoscopic approach was 12% as compared with 3% of robotic cases [46]. Similarly, Fornalik et al. reported no conversion during robotic staging of 76 women with BMI ≥40 kg/m^2. The authors could successfully perform pelvic and para-aortic lymphadenectomy in 96% vs 89% ($p = 0.2$) and 75% vs 60% ($p = 0.12$) of robotic versus laparotomy patients, respectively. Robotic surgery was associated with more lymph nodes collected with increasing BMI ($p < 0.001$) and decreased chances of ICU admissions [59]. The authors highlighted that the proficiency in doing adequate staging gets better in high volume centers. Contrarily, many studies and systematic reviews do not establish a significant improvement in the conversion rates and perioperative morbidity of robotic over laparoscopic surgery in obese and morbidly obese women (Table 7.4).

7.6.2 Cost of MIS

Despite all advantages of minimal invasive surgery, high cost is the major limitation of its adoption in third world countries. In a U.S. Nationwide Inpatient Sample database study, patients with low income, black or Hispanic race, Medicaid, and low volume treatment centers are less likely to get minimal access surgery owing to cost. Robotic hysterectomy was found to be $1291 more costly than conventional laparoscopy. There are several studies that evaluate the total cost or 30-day perioperative cost of open, laparoscopic and robotic surgery. The estimated cost varies in these studies and the cost difference cannot be generalized for each patient, as the cost of surgery depends on multiple factors like the complexity of case, type of hospital, room charges, cost of instrument and disposables, high or low volume center, associated complications, and the place of surgery (country and metro city). Most of the studies have reported higher costs for robotic surgery (Table 7.5). Few studies have suggested that overall 30-day cost is similar between robotic staging and open staging [86]. Surgery at a high volume center and more experience is associated with a reduction in the cost of robotic surgery [87].

One Indian study compared data on the use of analgesics, antiemetics, iv fluids, surgical time, blood loss, ICU stay, and duration of hospital stay in robotic versus open hysterectomy for endometrial cancer and atypical endometrial hyperplasia. As compared to open surgery, robotic surgery was associated with a total saving of $107.7 [88].

7.6.3 MIS in Elderly Women

The mean age of diagnosis of endometrial cancer is 62 years [89]. Advancing age is also a poor prognostic factor for survival. The reasons for poor prognosis are aggressive tumor biology, advanced disease, and poor tolerability to surgical and medical treatment. Elderly women are more prone to postoperative ileus, cardiorespiratory

Table 7.4 Conversions and wound complications in women with BMI > 30

Author	N	BMI	Conversion number (%)	Operating time mean (SD)/ median (range)	Estimated blood loss mean (SD)/ median (range)	Hospital stay mean (SD)/ median (range)	Wound complications number (%)
Holub (2000) [60]	CL 33	≥30	2/33 (6.06)	166.14	242.6 (50–1600)	5.3 (3–10)	1 (3.03)
Ghezzi (2006) [61]	CL 22	≥30	0/22 (0)	209 (49.1)	165 (50–400)	3 (2–6)	–
Eisenhauer (2007) [62]	OL154	≥35		40–368	40–2200	6 (4–56)	54 (35.06)
	Cl 25	≥35	4/25 (16)	940,330	50–500	3 (2–7)	2 (8)
Fanning (2010) [63]	CL 85	≥40	6/85 (7.05)	–	–	–	–
Cammani (2010) [64]	CL 10	≥30	0/10	178 (49)	–	–	–
Rabischong (2011) [65]	CL 52	≥30	2/52 (3.84)	187.5 (47.9)	–	5.2 (2.07)	–
Subramaniam (2011) [66]	OL 104	≥30		138.2 (53.4)	408.9 (290.3)	5.07 (2.54)	21 (20.19)
	RAL 73	≥30	9/73 (12.32)	246.2 (75.2)	95.9 (109.4)	2.73 (1.84)	3 (4.10)
Helm (2011) [67]	OL 56	≥36		–	–	–	–
	CL 29	≥36	5/29 (17.24)	–	–	–	–
Bigen (2011) [68]	OL 24	≥35		–	–	–	3 (12.5)
	CL 31	≥35	10/31 (32.25)	–	–	–	3 (9.67)
Tang (2012) [69]	OL 110	≥30		128 (39)	292 (226)	4.1 (2.2)	36 (32.72)
	RAL129	≥30	14/129 (10.85)	188 (63)	160 (150)	1.5 (1.0)	18 (13.95)
Bernardini (2012) [70]	OL 41	≥35		165 (75–295)	300 (100–350)	4 (2–21)	2 (4.87)
	RAL 45	≥35	4/45 (8.8)	270 (135–470)	200 (50–1500)	2 (1–24)	0 (0)
Farthing (2012) [71]	CL 61	30–39.99	1/61 (1.63)	95	50	2.5	2 (3.27)
	CL 53	≥40	1/53 (1.8)	75	50	2	1 (1.88)

Tinelli (2014) [72]	OL 30	≥35		143 (25)	155	6.3 (1.1)	3 (10)
	CL 45	≥35	0/45	166 (21)	80	3.1	3 (6.66)
Menderes (2014) [73]	RAL 135	30–39.99	1/135 (0.74)	162.6 (59)	120.2 (132.1)	1.59 (2.22)	–
	RAL 76	40–49.99		154.1 (49.2)	117.1 (83.2)	1.89 (3.1)	–
	RAL 28	≥50	1/76 (1.31)	188.95 (50.0)	152.7 (95.8)	2.07 (1.2)	–
Cunningham (2015) [74]	RAL 110	30–39	4/110 (3.63)	119.14	–	1.03	–
	RAL 101	≥40	8/101 (7.92)	129.6	–	1.08	–
Bige (2015) [75]	OL 70	≥35		185.94 (30.26)	438.29 (271.96)	10.36 (5.69)	8 (11.42)
	CL 70	≥35	6/70 (5.7)	155.03 (37.68)	561.86 (341.55)	4.64 (4.68)	1 (1.42)
Bouwman (2015) [76]	OL 110	30–40		–	290 (272.7)	–	–
	CL 81	30–40	16/81 (19.75)	–	116 (110.6)	–	–
	OL 36	≥40		–	258 (200.8)	–	–
	CL 33	≥40	9/33 (27.2)	–	125 (92.6)	–	–
Corrado (2015) [77]	RAL 50	40–45	0/50	162.5 (60–520)	75 (10–400)	3 (2–10)	1 (2)
	RAL 10	45–50	0/10	160 (80–330)	87.5 (20–200)	2 (2–4)	0 (0)
	RAL 10	≥50	0/10	177.5 (85–630)	50 (50–300)	3 (2–12)	0 (0)
Mendivil (2015) [78]	OL 24	≥40		81 (55.2–160.2)	250 (50–1000)	4 (2–25)	0 (0)
	CL 16	≥40	1/16 (6.25)	109.2 (66–235.2)	175 (24–700)	2 (1–4)	1 (6.25)
	RAL 13	≥40	1/13 (2.63)	166.8 (85.2–265.2)	100 (50–150)	2 (1–3)	0 (0)
Stephan (2015) [79]	RAL 56	≥50	11/56 (19.64)	269.1	150	2.1	7 (12.5)

(continued)

Table 7.4 (continued)

Author	N	BMI	Conversion number (%)	Operating time mean (SD)/ median (range)	Estimated blood loss mean (SD)/ median (range)	Hospital stay mean (SD)/ median (range)	Wound complications number (%)
Ucella (2015) [80]	CL 161	≥30		–	–	7.5 (6.2)	14 (8.69)
	CL 230	≥30	7/23 (3.04)	–	–	3.3 (2.5)	8 (3.47)
Cheng (2016) [81]	OL 60	≥40		261 (155–400)	188.2 (100–1000)	11 (7–17)	–
	CL 60	≥40	0/60	235 (160–360)	100.7 (30–500)	6 (4–7)	–
Hinshaw (2016) [82]	OL 80	≥35		200	338	4	7 (8.75)
	RAL 56	≥35	3/56 (5.35)	212	150	1	2 (3.57)
Leitao (2016) [46]	OL 299	≥40		170 (40–419)	250 (50–3000)	5 (2–37)	86 (23.76)
	CL 43	≥40	5/43 (11.62)	190 (89–354)	100 (25–900)	2 (1–7)	–
	RAL 90	≥40	3/90 (3.33)	193 (87–448)	50 (5–800)	1 (0–5)	–
Matsuo (2016) [83]	CL 97	30–39.99	6/97 (6.18)	–	–	–	–
	CL 66	≥40	14/66 (21.1)	–	–	–	–
Peng (2018) [84]	CL 70	30–39.99	7/70 (10)	185 (89)	191 (214)	–	4 (5.7)
	CL 31	≥40	1/31 (3.22)	181 (65)	119 (90)	–	2 (6

CL conventional laparoscopy, *RAL* robotic-assisted laparoscopy, *OL* open laparotomy

Table 7.5 Comparison of estimated total cost for open, laparoscopic and robotic surgery in endometrial cancer

Study	Number of cases in groups	Lap cost	Robotic cost	Open ($)
Bell et al. 2008 [27]	CL 30, RAL 40, OH 30	$7570	$8212	$12,944
Holtz et al. 2010 [33]	CL 20, RAL 13	$3615	$5084	–
Coronado et al. 2012 [37]	CL 84, RAL 71, OH 192	€4594	€5048	€4681
Wright et al. 2012 [47]	CL 1027, RAL 1437	$11,774	$10,176	$9618
Venkat et al. 2012 [38]	CL 27, RAL 37	$7981	$9519	–
Yu et al. 2013 [85]	CL 228, RAL 649, OH 1370	$37,202	$51,568	$36,492
Silva 2018 [50]	CLAL 43, RH 42	$6812	$9655	–

LH conventional laparoscopy, *RAL* robotic-assisted laparoscopy

complications, wound infections, and deep vein thrombosis. Trelendenberg position and cardiac compromise with high intra-abdominal pressure is also a challenge during minimal invasive surgery. Several retrospective studies have studied this population group and have revealed that minimal invasive surgery is feasible and well tolerated in elderly population [90–93].

Bishop et al. specifically analyzed 1477 EC patients ≥60 years who were enrolled in randomized control LAP-2 GOG clinical trial. Higher rates of recurrence and higher rates of death were observed due to disease in older population ($p < 0.001$). Higher rates of conversions were associated with increasing age (<50 years; 23.8% vs ≥80 years; 36.8%; $p = 0.003$ for all ages). Lymphadenectomy could not be accomplished in 4% of women ≥80 years who underwent open surgical staging. Otherwise, there was no significant difference in lymph node dissection rate by age for the entire population in the minimal invasive and open groups.

There were comparable intraoperative complications rates in the open group; however, there was significantly more propensity to develop postoperative complications after the age of 60 years. These complications include urinary tract infections, pneumonia, congestive heart failure, arrhythmia, DVT, readmission rate and treatment-related mortality. A linear model on the relationship of age with maximum toxicity of the surgical approach revealed that the toxicity appears to sharply increase after the age of 60 years ($p = 0.035$) (Fig. 7.2). This implies that true benefit is seen if minimal invasive surgery is done in elderly population.

Another study analyzed data of 1606 women ≥65 years who underwent staging surgery for endometrial cancer by the two approaches [94]. Multivariable analysis was done to correct for possible confounders and propensity scoring matching was done to take care of selection bias. 938 patients underwent laparoscopy and 668 patients underwent laparotomy. The incidence and severity of postoperative complications were significantly lower in women all class of elderly (≥65 years elderly, ≥75 years, very elderly, ≥80 years) who received minimal access surgery. A large retrospective study compared the perioperative safety of 7142 elderly women with endometrial cancer, managed by laparotomy and robotic surgery [95]. Robotic surgery was associated with improved perioperative outcome in elderly women.

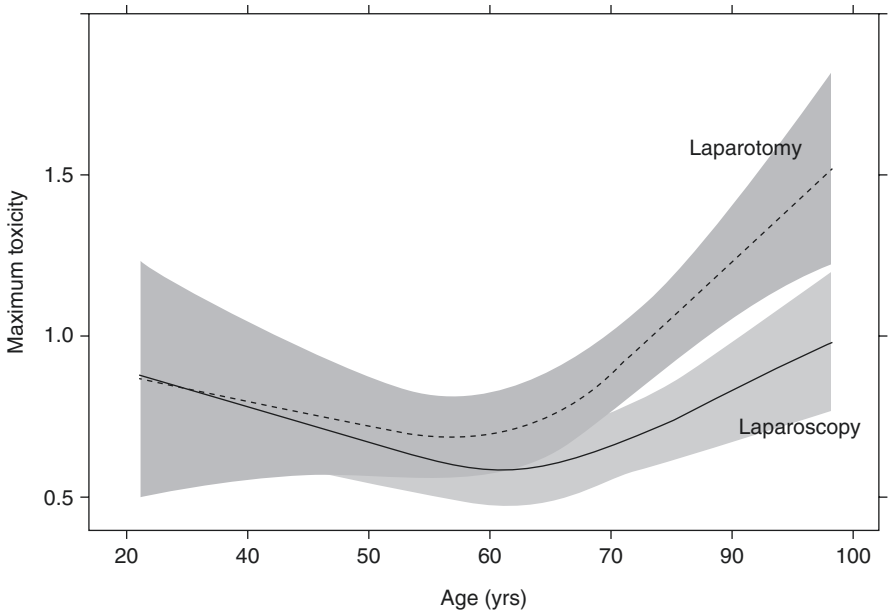


Fig. 7.2 Relationship between age and maximum toxicity for each treatment group. This is a linear model with outcome maximum toxicity. The model shows a treatment x age interaction with a moderate effect ($p = 0.035$). The effects plot suggests that the LAP group is prone to higher maximum toxicity after about age 60 (With Permission from Elsevier)

Several other studies demonstrate that minimal invasive surgery for endometrial cancer should be offered to elderly and very elderly women suffering from endometrial cancer [96, 97].

7.6.4 Use of Uterine Manipulator in MIS

A recent prospective randomized trial (Laparoscopic Approach to Cervical Cancer, LACC) has demonstrated significant inferiority of the minimal invasive approach in managing cervix cancer. The uterine manipulator is assumed to be the offending agent for such results. The available evidence in endometrial cancer suggests that use of uterine manipulator is not associated with poor outcome. It is worthy to note that the effects of uterine manipulation on the laparoscopic management of endometrial cancer were assessed in a randomized control trial [98]. 110 patients with endometrial cancer were randomized to laparoscopic staging with ($n = 55$) or without the RUMI manipulator ($n = 55$). Both groups had peritoneal cytology before and after the surgery. LVSI was compared between both the groups. The authors observed that the incidence of positive cytology and lympho-vascular space invasion was similar in both the groups. There was no difference in recurrences in a follow-up of 19 months [98]. Marcos et al. studied the recurrence rates and overall

survival rates in 147 women with endometrial cancer. The study incorporated clipping the fallopian tube before the procedure in both the groups. Karl storz manipulator was used in laparoscopic cases. Reassuringly the use of uterine manipulators in laparoscopic surgery patients was not associated with worse cumulative recurrence rates and overall survival rate [99]. Machida et al. illustrated that the use of v care manipulator in laparoscopic group was not associated with risk of lymphovascular invasion in a set of 687 women with endometrial cancer [100]. Another interesting study evaluated the risk and site of disease recurrence, overall survival, and disease-specific survival in women who has laparoscopic surgery with and without the use of uterine manipulator. The sample size consisted of 579 women in manipulator group and 372 women in whom manipulator was not used. Data was abstracted from seven Italian institutions, and multivariate analysis and propensity score matching were done. After a median follow-up of 49 months, there was insignificant differences in the disease-free, disease-specific, and overall survival [101]. Tinelli et al. also observed similar results in their study of 110 patients with endometrial cancer treated with open and minimal invasive surgery. It appears that for endometrial cancer, the tumor is contained inside the uterus and use of manipulator has little propensity to spill the tumor in peritoneal cavity.

7.6.5 Port Metastases in MIS

The rising utilization of minimal invasive surgery has led to more recognized cases of port-site metastasis. It is believed that tumor cell entrapment is an etiologic factor for PSM. Many times laparoscopic port sites get traumatized during tissue extraction and the high-pressure CO_2 escape increases the likelihood of wound implantation. Abu Rustum et al. studied 2593 laparoscopic procedures in 1288 women with gynecologic malignancy. They observed that laparoscopic subcutaneous tumor implantation was rare (0.97%) and was always associated with advanced peritoneal carcinomatosis. It was concluded that "the risk of subcutaneous tumor implantation should not be used as an argument against laparoscopy in the majority of women with gynecologic malignancies managed by gynecologic oncologists" [102]. Martinez evaluated the overall incidence of PSM in 1216 laparoscopic procedures for cervix cancer and 295 women with endometrial cancer. The incidence of PSM in women with endometrial cancer was 0.33%. Excluding the patients with peritoneal metastases the PSM reduced to 0% [103]. A review of published case reports on the incidence of PSM in women undergoing minimal invasive surgery for endometrial cancer demonstrated its rare occurrence; only 12 port-site recurrences were identified (4 cases isolated and 8 non-isolated). The authors of the case reports have hypothesized difficult uterine extraction, uterine perforation, ascites, and peritoneal carcinomatosis as the possible etiology [104]. In absence of definitive concluding evidence, the advantages of minimal invasive surgery cannot be disregarded for a rare adverse event.

7.7 Conclusion

Appraisal of the evidence suggests that minimal invasive surgery has fewer short-term complications and has just as good long-term safety as an open surgery. Robotic approach is found to be favorable for obese and elderly women. There is no evidence of higher recurrence associated with manipulator use. Barriers for utilization of minimal access surgery in endometrial cancer should be identified and it should be available as a choice for most women.

7.8 Key Points

- Minimal access surgery is recommended route for management of early-stage endometrial cancer.
- Minimal access surgery is associated with faster recovery, lesser blood loss, lesser postoperative complications.
- Nine randomized trials have demonstrated non-inferiority of laparoscopic surgery over open surgery in the treatment of endometrial cancer.
- Laparoscopic single-site surgery and single-port robotic approach are feasible for endometrial cancer staging procedure, but has a longer learning curve and longer duration of surgery with minimal advantage over conventional laparoscopy.
- Only RCT comparing outcome of conventional laparoscopy to robotic surgery has demonstrated significantly longer duration of surgery and more conversions to laparotomy. The duration of hospital stay and lymph node yields are equivalent in both the MIS approaches.
- MIS is advantageous for elderly and obese population and should be offered to these women if eligible.
- Robotic surgery is found to be more expensive as compared to conventional laparoscopy, owing to set up investment and cost of disposables.
- The use of uterine manipulator during minimal invasive surgery is not associated with higher recurrence.

References

1. Zullo F, Palomba S, Falbo A, Russo T, Mocciaro R, Tartaglia E, et al. Laparoscopic surgery vs laparotomy for early stage endometrial cancer: long-term data of a randomized controlled trial. Am J Obstet Gynecol. 2009 Mar;200(3):296–9.
2. Park DA, Lee DH, Kim SW, Lee SH. Comparative safety and effectiveness of robot-assisted laparoscopic hysterectomy versus conventional laparoscopy and laparotomy for endometrial cancer: a systematic review and meta-analysis. Eur J Surg Oncol. 2016 Sep;42(9):1303–14.
3. Burke WM, Orr J, Leitao M, Salom E, Gehrig P, Olawaiye AB, et al. Endometrial cancer: a review and current management strategies: part I. Gynecol Oncol. 2014 Aug;134(2):385–92.
4. Practice Bulletin No. 149. Endometrial cancer. Obstet Gynecol. 2015 Apr;125(4):1006–26.

5. Bean S, Bradley K, Campos SM, Cho KR, Chon HS, Chu C, et al. Uterine neoplasms. J Natl Compr Canc Netw. 2018;2:170–99.
6. Childers JM, Surwit EA. Combined laparoscopic and vaginal surgery for the management of two cases of stage I endometrial cancer. Gynecol Oncol. 1992;45(1):46–51.
7. Childers JM, Brzechffa PR, Hatch KD, Surwit EA. Laparoscopically assisted surgical staging (LASS) of endometrial cancer. Gynecol Oncol. 1993;51:33.
8. 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.
9. Scribner DR, Walker JL, Johnson GA, McMeekin SD, Gold MA, Mannel RS. Surgical management of early-stage endometrial cancer in the elderly: is laparoscopy feasible? Gynecol Oncol. 2001;83(3):563–8.
10. Barnett JC, Havrilesky LJ, Bondurant AE, Fleming ND, Lee PS, Secord AA, et al. Adverse events associated with laparoscopy vs laparotomy in the treatment of endometrial cancer. Am J Obstet Gynecol. 2011;205(2):143.
11. 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.
12. Walker JL, Piedmonte MR, Spirtos NM, Eisenkop SM, Schlaerth JB, Mannel RS, 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.
13. Fram KM. Laparoscopically assisted vaginal hysterectomy versus abdominal hysterectomy in stage I endometrial cancer. Int J Gynecol Cancer. 2002;12(1):57–61.
14. Janda M, Gebski V, Brand A, Hogg R, Jobling TW, Land R, et al. Quality of life after total laparoscopic hysterectomy versus total abdominal hysterectomy for stage I endometrial cancer (LACE): a randomised trial. Lancet Oncol. 2010 Aug;11(8):772–80.
15. Janda M, Gebski V, Davies LC, Forder P, Brand A, Hogg R, et al. Effect of total laparoscopic hysterectomy vs total abdominal hysterectomy on disease-free survival among women with stage I endometrial cancer: a randomized clinical trial. JAMA. 2017 Mar;317(12):1224–33.
16. Lu Q, Liu H, Liu C, Wang S, Li S, Guo S, et al. Comparison of laparoscopy and laparotomy for management of endometrial carcinoma: a prospective randomized study with 11-year experience. J Cancer Res Clin Oncol. 2013 Nov;139(11):1853–9.
17. Malzoni M, Tinelli R, Cosentino F, Perone C, Rasile M, Iuzzolino D, et al. Total laparoscopic hysterectomy versus abdominal hysterectomy with lymphadenectomy for early-stage endometrial cancer: a prospective randomized study. Gynecol Oncol. 2009 Jan;112(1):126–33.
18. Bijen CBM, Briet JM, de Bock GH, Arts HJG, Bergsma-Kadijk JA, Mourits MJE. Total laparoscopic hysterectomy versus abdominal hysterectomy in the treatment of patients with early stage endometrial cancer: a randomized multi center study. BMC Cancer. 2009 Jan;9:23.
19. Mourits MJE, Bijen CB, Arts HJ, ter Brugge HG, van der Sijde R, Paulsen L, et al. Safety of laparoscopy versus laparotomy in early-stage endometrial cancer: a randomised trial. Lancet Oncol. 2010 Aug;11(8):763–71.
20. Tozzi R, Malur S, Koehler C, Schneider A. Laparoscopy versus laparotomy in endometrial cancer: first analysis of survival of a randomized prospective study. J Minim Invasive Gynecol. 2005;12(2):130–6.
21. Galaal K, Donkers H, Bryant A, Lopes AD. Laparoscopy versus laparotomy for the management of early stage endometrial cancer. Cochrane Database Syst Rev. 2018 Oct;10:CD006655.
22. Fagotti A, Boruta DM 2nd, Scambia G, Fanfani F, Paglia A, Escobar PF. First 100 early endometrial cancer cases treated with laparoendoscopic single-site surgery: a multicentric retrospective study. Am J Obstet Gynecol. 2012 Apr;206(4):353–6.
23. Zapardiel I, Moreno E, Pinera A, De Santiago J. Novel technique for the complete staging of endometrial cancer by single-port laparoscopy. Gynecol Oncol. 2016 Feb;140(2):369–71.
24. Park J-Y, Kim D-Y, Suh D-S, Kim J-H, Nam J-H. Laparoendoscopic single-site versus conventional laparoscopic surgical staging for early-stage endometrial cancer. Int J Gynecol Cancer. 2014 Feb;24(2):358–63.

25. Reynolds RK, Burke WM, Advincula AP. Preliminary experience with robot-assisted laparoscopic staging of gynecologic malignancies. JSLS. 2005;9(2):149.
26. Boggess JF, Gehrig PA, Cantrell L, Shafer A, Ridgway M, Skinner EN, et al. A comparative study of 3 surgical methods for hysterectomy with staging for endometrial cancer: robotic assistance, laparoscopy, laparotomy. Am J Obstet Gynecol. 2008 Oct;199(4):360–9.
27. Bell MC, Torgerson J, Seshadri-Kreaden U, Suttle AW, Hunt S. Comparison of outcomes and cost for endometrial cancer staging via traditional laparotomy, standard laparoscopy and robotic techniques. Gynecol Oncol. 2008 Dec;111(3):407–11.
28. Magrina JF, Kho RM, Weaver AL, Montero RP, Magtibay PM. Robotic radical hysterectomy: comparison with laparoscopy and laparotomy. Gynecol Oncol. 2008 Apr;109(1):86–91.
29. 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 Oct;111(1):41–5.
30. Veljovich DS, Paley PJ, Drescher CW, Everett EN, Shah C, Peters WA 3rd. Robotic surgery in gynecologic oncology: program initiation and outcomes after the first year with comparison with laparotomy for endometrial cancer staging. Am J Obstet Gynecol. 2008 Jun;198(6):679.e1–e9; discussion 679.e9–10.
31. Seamon LG, Bryant SA, Rheaume PS, Kimball KJ, Huh WK, Fowler JM, et al. Comprehensive surgical staging for endometrial cancer in obese patients: comparing robotics and laparotomy. Obstet Gynecol. 2009 Jul;114(1):16–21.
32. Cardenas-Goicoechea J, Adams S, Bhat SB, Randall TC. Surgical outcomes of robotic-assisted surgical staging for endometrial cancer are equivalent to traditional laparoscopic staging at a minimally invasive surgical center. Gynecol Oncol. 2010 May;117(2):224–8.
33. Holtz DO, Miroshnichenko G, Finnegan MO, Chernick M, Dunton CJ. Endometrial cancer surgery costs: robot vs laparoscopy. J Minim Invasive Gynecol. 2010;17(4):500–3.
34. Jung YW, Lee DW, Kim SW, Nam EJ, Kim JH, Kim JW, et al. Robot-assisted staging using three robotic arms for endometrial cancer: comparison to laparoscopy and laparotomy at a single institution. J Surg Oncol. 2010 Feb;101(2):116–21.
35. Lim PC, Kang E, Park DH. Learning curve and surgical outcome for robotic-assisted hysterectomy with lymphadenectomy: case-matched controlled comparison with laparoscopy and laparotomy for treatment of endometrial cancer. J Minim Invasive Gynecol. 2010;17(6):739–48.
36. Shah NT, Wright KN, Jonsdottir GM, Jorgensen S, Einarsson JI, Muto MG. The feasibility of societal cost equivalence between robotic hysterectomy and alternate hysterectomy methods for endometrial cancer. Obstet Gynecol Int. 2011;2011:570464.
37. Coronado PJ, Herraiz MA, Magrina JF, Fasero M, Vidart JA. Comparison of perioperative outcomes and cost of robotic-assisted laparoscopy, laparoscopy and laparotomy for endometrial cancer. Eur J Obstet Gynecol Reprod Biol. 2012 Dec;165(2):289–94.
38. Venkat P, Chen L-M, Young-Lin N, Kiet TK, Young G, Amatori D, et al. An economic analysis of robotic versus laparoscopic surgery for endometrial cancer: costs, charges and reimbursements to hospitals and professionals. Gynecol Oncol. 2012 Apr;125(1):237–40.
39. Escobar PF, Frumovitz M, Soliman PT, Frasure HE, Fader AN, Schmeler KM, et al. Comparison of single-port laparoscopy, standard laparoscopy, and robotic surgery in patients with endometrial cancer. Ann Surg Oncol. 2012 May;19(5):1583–8.
40. Turunen H, Pakarinen P, Sjoberg J, Loukovaara M. Laparoscopic vs robotic-assisted surgery for endometrial carcinoma in a centre with long laparoscopic experience. J Obstet Gynaecol. 2013 Oct;33(7):720–4.
41. Seror J, Bats A-S, Huchon C, Bensaid C, Douay-Hauser N, Lecuru F. Laparoscopy vs robotics in surgical management of endometrial cancer: comparison of intraoperative and postoperative complications. J Minim Invasive Gynecol. 2014;21(1):120–5.
42. Chiou H-Y, Chiu L-H, Chen C-H, Yen Y-K, Chang C-W, Liu W-M. Comparing robotic surgery with laparoscopy and laparotomy for endometrial cancer management: a cohort study. Int J Surg. 2015 Jan;13:17–22.

43. Barrie A, Freeman AH, Lyon L, Garcia C, Conell C, Abbott LH, et al. Classification of post-operative complications in robotic-assisted compared with laparoscopic hysterectomy for endometrial cancer. J Minim Invasive Gynecol. 2016 Nov;23(7):1181–8.
44. Johnson L, Bunn WD, Nguyen L, Rice J, Raj M, Cunningham MJ. Clinical comparison of robotic, laparoscopic, and open hysterectomy procedures for endometrial cancer patients. J Robot Surg. 2017 Sep;11(3):291–7.
45. Mäenpää MM, Nieminen K, Tomás EI, Laurila M. For endometrial cancer: a randomized controlled trial. Am J Obstet Gynecol. 2016;215(5):588.e1–7. https://doi.org/10.1016/j.ajog.2016.06.005.
46. Leitao MM, Narain WR, Boccamazzo D, Sioulas V, Cassella D, Ducie JA, et al. Impact of robotic platforms on surgical approach and costs in the management of morbidly obese patients with newly diagnosed uterine cancer. Ann Surg Oncol. 2016 Jul;23(7):2192–8.
47. Wright JD, Burke WM, Wilde ET, Lewin SN, Charles AS, Kim JH, et al. Comparative effectiveness of robotic versus laparoscopic hysterectomy for endometrial cancer. J Clin Oncol. 2012;30(8):783.
48. Mäenpää MM, Nieminen K, Tomás EI, Laurila M, Luukkaala TH, Mäenpää JU. Robotic-assisted vs traditional laparoscopic surgery for endometrial cancer: a randomized controlled trial. Am J Obstet Gynecol. 2016 Nov [cited 2018 Feb 9];215(5):588.e1–7. http://www.ncbi.nlm.nih.gov/pubmed/27288987
49. Cardenas-Goicoechea J, Shepherd A, Momeni M, Mandeli J, Chuang L, Gretz H, et al. Survival analysis of robotic versus traditional laparoscopic surgical staging for endometrial cancer. Am J Obstet Gynecol. 2014 Feb;210(2):160.e1–160.e11.
50. Silva E, Silva A, de Carvalho JPM, Anton C, Fernandes RP, Baracat EC, Carvalho JP. Introduction of robotic surgery for endometrial cancer into a Brazilian cancer service: a randomized trial evaluating perioperative clinical outcomes and costs. Clinics (Sao Paulo). 2018 Sep;73(suppl 1):e522s.
51. Kilgore JE, Jackson AL, Ko EM, Soper JT, Van Le L, Gehrig PA, et al. Recurrence-free and 5-year survival following robotic-assisted surgical staging for endometrial carcinoma. Gynecol Oncol. 2013;129:49.
52. Park HK, Helenowski IB, Berry E, Lurain JR, Neubauer NL. A comparison of survival and recurrence outcomes in patients with endometrial cancer undergoing robotic versus open surgery. J Minim Invasive Gynecol. 2015;22(6):961–7.
53. Chen S-H, Li Z-A, Huang R, Xue H-Q. Robot-assisted versus conventional laparoscopic surgery for endometrial cancer staging: a meta-analysis. Taiwan J Obstet Gynecol. 2016 Aug;55(4):488–94.
54. Ind T, Laios A, Hacking M, Nobbenhuis M. A comparison of operative outcomes between standard and robotic laparoscopic surgery for endometrial cancer: a systematic review and meta-analysis. Int J Med Robot. 2017 Dec;13(4):e1851.
55. Yoon A, Yoo H-N, Lee Y-Y, Lee J-W, Kim B-G, Bae D-S, et al. Robotic single-port hysterectomy, adnexectomy, and lymphadenectomy in endometrial cancer. J Minim Invasive Gynecol. 2015;22(3):322.
56. Mereu L, Carri G, Khalifa H. Robotic single port total laparoscopic hysterectomy for endometrial cancer patients. Gynecol Oncol. 2012 Dec;127(3):644.
57. Chung H, Jang T-K, Nam SH, Kwon S-H, Shin S-J, Cho C-H. Robotic single-site staging operation for early-stage endometrial cancer: initial experience at a single institution. Obstet Gynecol Sci. 2019 May;62(3):149–56.
58. Sinno AK, Fader AN, Tanner EJ 3rd. Single site robotic sentinel lymph node biopsy and hysterectomy in endometrial cancer. Gynecol Oncol. 2015 Apr;137(1):190.
59. Fornalik H, Zore T, Fornalik N, Foster T, Katschke A, Wright G. Can teamwork and high-volume experience overcome challenges of lymphadenectomy in morbidly obese patients (body mass index of 40 kg/m2 or greater) with endometrial cancer?: A cohort study of robotics and laparotomy and review of literature. Int J Gynecol Cancer. 2018 Jun;28(5):959–66.
60. Holub Z, Bartos P, Jabor A, Eim J, Fischlova D, Kliment L. Laparoscopic surgery in obese women with endometrial cancer. J Am Assoc Gynecol Laparosc. 2000 Feb;7(1):83–8.

61. Ghezzi F, Cromi A, Bergamini V, Uccella S, Beretta P, Franchi M, et al. Laparoscopic management of endometrial cancer in nonobese and obese women: a consecutive series. J Minim Invasive Gynecol. 2006;13(4):269–75.
62. Eisenhauer EL, Wypych KA, Mehrara BJ, Lawson C, Chi DS, Barakat RR, et al. Comparing surgical outcomes in obese women undergoing laparotomy, laparoscopy, or laparotomy with panniculectomy for the staging of uterine malignancy. Ann Surg Oncol. 2007 Aug;14(8):2384–91.
63. Fanning J, Hossler C. Laparoscopic conversion rate for uterine cancer surgical staging. Obstet Gynecol. 2010 Dec;116(6):1354–7.
64. Camanni M, Bonino L, Delpiano EM, Migliaretti G, Berchialla P, Deltetto F. Laparoscopy and body mass index: feasibility and outcome in obese patients treated for gynecologic diseases. J Minim Invasive Gynecol. 2010;17(5):576–82.
65. Rabischong B, Larrain D, Canis M, Le Bouedec G, Pomel C, Jardon K, et al. Long-term follow-up after laparoscopic management of endometrial cancer in the obese: a fifteen-year cohort study. J Minim Invasive Gynecol. 2011;18(5):589–96.
66. Subramaniam A, Kim KH, Bryant SA, Zhang B, Sikes C, Kimball KJ, et al. A cohort study evaluating robotic versus laparotomy surgical outcomes of obese women with endometrial carcinoma. Gynecol Oncol. 2011 Sep;122(3):604–7.
67. Helm CW, Arumugam C, Gordinier ME, Metzinger DS, Pan J, Rai SN. Laparoscopic surgery for endometrial cancer: increasing body mass index does not impact postoperative complications. J Gynecol Oncol. 2011 Sep;22(3):168–76.
68. Bijen CBM, de Bock GH, Vermeulen KM, Arts HJG, ter Brugge HG, van der Sijde R, et al. Laparoscopic hysterectomy is preferred over laparotomy in early endometrial cancer patients, however not cost effective in the very obese. Eur J Cancer. 2011 Sep;47(14):2158–65.
69. Tang KY, Gardiner SK, Gould C, Osmundsen B, Collins M, Winter WE 3rd. Robotic surgical staging for obese patients with endometrial cancer. Am J Obstet Gynecol. 2012 Jun;206(6):513.e1–6.
70. Bernardini MQ, Gien LT, Tipping H, Murphy J, Rosen BP. Surgical outcome of robotic surgery in morbidly obese patient with endometrial cancer compared to laparotomy. Int J Gynecol Cancer. 2012 Jan;22(1):76–81.
71. Farthing A, Chatterjee J, Joglekar-Pai P, Dorney E, Ghaem-Maghami S. Total laparoscopic hysterectomy for early stage endometrial cancer in obese and morbidly obese women. J Obstet Gynaecol. 2012 Aug;32(6):580–4.
72. Tinelli R, Litta P, Meir Y, Surico D, Leo L, Fusco A, et al. Advantages of laparoscopy versus laparotomy in extremely obese women (BMI>35) with early-stage endometrial cancer: a multicenter study. Anticancer Res. 2014 May;34(5):2497–502.
73. Menderes G, Azodi M, Clark L, Xu X, Lu L, Ratner E, et al. Impact of body mass index on surgical outcomes and analysis of disease recurrence for patients with endometrial cancer undergoing robotic-assisted staging. Int J Gynecol Cancer. 2014 Jul;24(6):1118–25.
74. Cunningham MJ, Dorzin E, Nguyen L, Anderson E, Bunn WDJ. Body mass index, conversion rate and complications among patients undergoing robotic surgery for endometrial carcinoma. J Robot Surg. 2015 Dec;9(4):339–45.
75. Bige O, Demir A, Saatli B, Koyuncuoglu M, Saygili U. Laparoscopy versus laparotomy for the management of endometrial carcinoma in morbidly obese patients: a prospective study. J Turkish Ger Gynecol Assoc. 2015;16(3):164–9.
76. Bouwman F, Smits A, Lopes A, Das N, Pollard A, Massuger L, et al. The impact of BMI on surgical complications and outcomes in endometrial cancer surgery--an institutional study and systematic review of the literature. Gynecol Oncol. 2015 Nov;139(2):369–76.
77. Corrado G, Chiantera V, Fanfani F, Cutillo G, Lucidi A, Mancini E, et al. Robotic hysterectomy in severely obese patients with endometrial cancer: a multicenter study. J Minim Invasive Gynecol. 2016 Jan;23(1):94–100.
78. Mendivil AA, Rettenmaier MA, Abaid LN, Brown JV 3rd, Micha JP, Lopez KL, et al. A comparison of open surgery, robotic-assisted surgery and conventional laparoscopic surgery in the treatment of morbidly obese endometrial cancer patients. JSLS. 2015;19(1):e2014.00001.

79. Stephan J-M, Goodheart MJ, McDonald M, Hansen J, Reyes HD, Button A, et al. Robotic surgery in supermorbidly obese patients with endometrial cancer. Am J Obstet Gynecol. 2015 Jul;213(1):49.e1–8.
80. Uccella S, Bonzini M, Palomba S, Fanfani F, Ceccaroni M, Seracchioli R, et al. Impact of obesity on surgical treatment for endometrial cancer: a multicenter study comparing laparoscopy vs open surgery, with propensity-matched analysis. J Minim Invasive Gynecol. 2016 Jan;23(1):53–61.
81. Cheng Z, He X, Zhao A, Zhang Q, Li Y. Early endometrial carcinoma therapy in morbid obesity: a retrospective study comparing open and laparoscopic. Int J Surg. 2016 Jun;30:31–4.
82. Hinshaw SJ, Gunderson S, Eastwood D, Bradley WH. Endometrial carcinoma: the perioperative and long-term outcomes of robotic surgery in the morbidly obese. J Surg Oncol. 2016 Dec;114(7):884–7.
83. Matsuo K, Jung CE, Hom MS, Gualtieri MR, Randazzo SC, Kanao H, et al. Predictive factor of conversion to laparotomy in minimally invasive surgical staging for endometrial cancer. Int J Gynecol Cancer. 2016 Feb;26(2):290–300.
84. Peng J, Sinasac S, Pulman KJ, Zhang L, Murphy J, Feigenberg T. The feasibility of laparoscopic surgery in gynecologic oncology for obese and morbidly obese patients. Int J Gynecol Cancer. 2018 Jun;28(5):967–74.
85. Yu X, Lum D, Kiet TK, Fuh KC, Orr JJ, Brooks RA, et al. Utilization of and charges for robotic versus laparoscopic versus open surgery for endometrial cancer. J Surg Oncol. 2013 May;107(6):653–8.
86. Bogani G, Multinu F, Dowdy SC, Cliby WA, Wilson TO, Gostout BS, et al. Incorporating robotic-assisted surgery for endometrial cancer staging: analysis of morbidity and costs. Gynecol Oncol. 2016 May;141(2):218–24.
87. Avondstondt AM, Wallenstein M, D'Adamo CR, Ehsanipoor RM. Change in cost after 5 years of experience with robotic-assisted hysterectomy for the treatment of endometrial cancer. J Robot Surg. 2018 Mar;12(1):93–6.
88. Agarwal R, Rajanbabu A, Unnikrishnan UG. A retrospective evaluation of the perioperative drug use and comparison of its cost in robotic vs open surgery for endometrial cancer. J Robot Surg. 2018 Dec;12(4):665–72.
89. Duska L, Shahrokni A, Powell M. Treatment of older women with endometrial cancer: improving outcomes with personalized care. Am Soc Clin Oncol Educ Book. 2019;36:164–74.
90. Frey MK, Ihnow SB, Worley MJJ, Heyman KP, Kessler R, Slomovitz BM, et al. Minimally invasive staging of endometrial cancer is feasible and safe in elderly women. J Minim Invasive Gynecol. 2011;18(2):200–4.
91. Lavoue V, Zeng X, Lau S, Press JZ, Abitbol J, Gotlieb R, et al. Impact of robotics on the outcome of elderly patients with endometrial cancer. Gynecol Oncol. 2014 Jun;133(3):556–62.
92. Vaknin Z, Perri T, Lau S, Deland C, Drummond N, Rosberger Z, et al. Outcome and quality of life in a prospective cohort of the first 100 robotic surgeries for endometrial cancer, with focus on elderly patients. Int J Gynecol Cancer. 2010 Nov;20(8):1367–73.
93. Bishop EA, Java JJ, Moore KN, Spirtos NM, Pearl ML, Zivanovic O, et al. Surgical outcomes among elderly women with endometrial cancer treated by laparoscopic hysterectomy: a NRG/Gynecologic Oncology Group study. Am J Obstet Gynecol. 2018 Jan;218(1):109.e1–109.e11.
94. Uccella S, Bonzini M, Palomba S, Fanfani F, Malzoni M, Ceccaroni M, et al. Laparoscopic vs. open treatment of endometrial cancer in the elderly and very elderly: an age-stratified multicenter study on 1606 women. Gynecol Oncol. 2016 May;141(2):211–7.
95. Guy MS, Sheeder J, Behbakht K, Wright JD, Guntupalli SR. Comparative outcomes in older and younger women undergoing laparotomy or robotic surgical staging for endometrial cancer. Am J Obstet Gynecol. 2016 Mar;214(3):350.e1–350.e10.
96. Bourgin C, Lambaudie E, Houvenaeghel G, Foucher F, Leveque J, Lavoue V. Impact of age on surgical staging and approaches (laparotomy, laparoscopy and robotic surgery) in endometrial cancer management. Eur J Surg Oncol. 2017 Apr;43(4):703–9.

97. Doo DW, Guntupalli SR, Corr BR, Sheeder J, Davidson SA, Behbakht K, et al. Comparative surgical outcomes for endometrial cancer patients 65 years old or older staged with robotics or laparotomy. Ann Surg Oncol. 2015 Oct;22(11):3687–94.
98. Lee M, Kim YT, Kim SW, Kim S, Kim JH, Nam EJ. Effects of uterine manipulation on surgical outcomes in laparoscopic management of endometrial cancer: a prospective randomized clinical trial. Int J Gynecol Cancer. 2013 Feb;23(2):372–9.
99. Marcos-Sanmartin J, Lopez Fernandez JA, Sanchez-Paya J, Pinero-Sanchez OC, Roman-Sanchez MJ, Quijada-Cazorla MA, et al. Does the type of surgical approach and the use of uterine manipulators influence the disease-free survival and recurrence rates in early-stage endometrial cancer? Int J Gynecol Cancer. 2016 Nov;26(9):1722–6.
100. Machida H, Hom MS, Adams CL, Eckhardt SE, Garcia-Sayre J, Mikami M, et al. Intrauterine manipulator use during minimally invasive hysterectomy and risk of lymphovascular space invasion in endometrial cancer. Int J Gynecol Cancer. 2018 Feb;28(2):208–19.
101. Uccella S, Bonzini M, Malzoni M, Fanfani F, Palomba S, Aletti G, et al. The effect of a uterine manipulator on the recurrence and mortality of endometrial cancer: a multi-centric study by the Italian Society of Gynecological Endoscopy. Am J Obstet Gynecol. 2017 Jun;216(6):592.e1–592.e11.
102. Abu-Rustum NR, Rhee EH, Chi DS, Sonoda Y, Gemignani M, Barakat RR. Subcutaneous tumor implantation after laparoscopic procedures in women with malignant disease. Obstet Gynecol. 2004 Mar;103(3):480–7.
103. Martinez A, Querleu D, Leblanc E, Narducci F, Ferron G. Low incidence of port-site metastases after laparoscopic staging of uterine cancer. Gynecol Oncol. 2010 Aug;118(2):145–50.
104. Palomba S, Falbo A, Russo T, La Sala GB. Port-site metastasis after laparoscopic surgical staging of endometrial cancer: a systematic review of the published and unpublished data. J Minim Invasive Gynecol. 2012;19(4):531–7.

8 Review: Clinical Trials Outcome for Chemotherapy in Endometrial Cancer

Abhishek Malakar, Anshul Grover, and Ritu Khatuja

8.1 Introduction

Clinical trials are research work involving people and treatment. These are mainly done to test the safety and efficacy of any new treatment. Clinical trials are done in four different phases to answer four different aspects, i.e., Phase I to see safety, Phase II to see effectiveness, Phase III to compare with other available treatment options, and Phase IV to see other uses of the treatment [1]. Globally endometrial cancer accounts for 5.3% of cancers affecting women [2]. It is proposed that an estimated 61,880 new cases of endometrial cancer will be detected in the United States and 12,160 women will die of uterine corpus cancer in 2019–2020. Since 2006, the incidence of endometrial cancer has increased by 1% per year in the white population and by 2% per year in the black population in the United States with an increase in its mortality rates by 2% in both [3].

Endometrial cancer is classified into different stages on the basis of the microscopic pattern and the ability of the tumor to invade the uterine muscle. This also determines the risk of recurrence of the tumor. Endometrioid adenocarcinoma is the most common pathological type of endometrial cancer. About 10% of all endometrial cancers are of clear cell and serous type and a small proportion are of mixed Mullerian tumor also known as carcinosarcoma [4]. These tumors are more aggressive and associated with poor prognosis. The risk stratification of tumors is based on FIGO staging and histopathological factors and includes tumor grade, tumor size, cell type, depth of myometrial invasion, presence of lymphovascular space invasion (LVSI), and staging [5, 6]. The women with stages I and II disease are classified into

A. Malakar · R. Khatuja (✉)
Department of Obstetrics & Gynecology, ANIIMS & G B Pant Hospital, Port Blair, Andaman & Nicobar Islands, India

A. Grover
Department of Obstetrics & Gynecology, Babu Jagjivanram Memorial Hospital, New Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_8

low, intermediate, and high risk [7]. The presence of risk factors increases the incidence of micrometastasis.

Low Risk This group includes women with disease confined to the endometrium, with well or moderately differentiated endometrioid tumors. They have an extremely low risk of nodal metastases [8]. These women are usually cured with hysterectomy alone. They do not require adjuvant chemotherapy, but need careful surveillance in the post-surgery period.

Intermediate Risk This group composed of women in stage I/II with myometrial invasion or those with disease extending into the cervical stroma. This group is further divided into low intermediate risk and high intermediate risk (HIR) based on the analysis of patients recruited in the protocol of the study by Gynaecology oncology group (GOG) 99 [6]. The criteria for the HIR group are defined according to age, and presence of three histopathological findings—histological tumor grading 2/3, lymphovascular space invasion, and myometrial space invasion of the outer third of myometrium.

- Women older than 70 years, with one of the pathological criteria
- Women aged 50–69 years, with two of the three pathological criteria
- Women aged less than 50 years, with all three pathological criteria [6]

A small proportion of these tumors have the ability to recur. HIR patients have been found to benefit from adjuvant external beam radiation therapy, but no such benefit of any kind of adjuvant therapy was seen in the low intermediate-risk group.

High-Risk Group This group includes patients with serous and clear cell adenocarcinoma or those with early-stage high grade or deeply invasive cancer. These tumors are associated with increased incidence of recurrence. It is this subset of tumors that are known to respond to adjuvant therapy.

This growing burden of endometrial cancer is the basis behind the rapidly evolving treatment protocols. Surgical management has been the mainstay especially in the early stages of endometrial cancer. However, many advanced-stage and some high-risk early-stage cancers will recur and presently our focus is to learn postoperative adjuvant treatment options, so as to provide better management to improve the progression-free survival (PFS).

8.2 Reason to Evaluate Role of Chemotherapy with Clinical Trials in Endometrial Carcinoma

Postoperative chemotherapy demands evaluation with clinical trials because

- Multiple case series have documented the sensitivity of chemotherapy in advanced and recurrent cancers. Humber et al. in a Cochrane meta-analysis of 11 trials of 2288 patients with advanced endometrial cancer inferred that chemotherapy improved the progression-free survival [9].

- Chemotherapy is extremely toxic and increases the expenses of the treatment. Any potential benefit of disease-free survival needs to be weighed against the toxicity associated with it.
- Radiotherapy has the potential to eliminate the residual postoperative disease, but only in its field of treatment, while systemic chemotherapeutic agents have the ability to target micrometastasis outside the field of chemotherapy to reduce postoperative recurrences. Patients with high-risk disease diagnosed postoperatively are benefited most with adjuvant chemotherapy.

Chemotherapy in endometrial cancer can be used as adjuvant, neoadjuvant, or as radiosensitizer. The aim is to reduce the risk of disease recurrence and distant metastases. The treatment is guided by surgical stage, tumor histology, and the number of adverse risk factors. All chemotherapeutic agents are associated with an increased incidence of toxicity. Continued trials of different newer chemotherapeutic agents, as well as newer targeted agents, are on, in search of a safe as well as an effective and safe therapeutic option. Results of some newer trials have been published and many more trials are still ongoing, which will definitely be of great help in the field of gynecological oncology in the near future. Other than the conventional chemotherapy and hormonal therapy, a newer concept of targeted therapy is suggested for postoperative treatment of endometrial cancer.

8.3 Role of Adjuvant Therapy in Early-Stage Disease (Stages I and II)

Adjuvant therapy for early-stage disease is proposed for the subset of patients who are at increased risk of developing micrometastatic disease.

Adjuvant radiotherapy was administered to patients with early-stage endometrial carcinoma with poor prognostic factors, but three large prospective randomized trials failed to demonstrate any survival benefit, while demonstrating improvement in pelvic recurrences. These trials received criticism from the researchers for low numbers of the study population. These were the *GOG 99, PORTEC-1* (Postoperative Radiotherapy in Endometrial Cancer), and ASTEN/EN.5 trials [6, 7, 10].

GOG 99 study was conducted by Keys et al. in 392 patients of intermediate-risk from 1987–1995 by subjecting them to an observation arm and radiation arm with 50.5 Gray (Gy). The outcome measures studied were primary toxicity, location and time of recurrence and overall survival (OS). The study classified the risk factors as mentioned. The 2-year cumulative risk of recurrence was 12% in observation group versus 3% in radiation group. In the high-risk group also the advantage of adjuvant radiotherapy was reflected (26% versus 6%). No difference was observed in the overall survival (OS) in both groups. It concluded that adjuvant therapy decreases the risk of recurrence but not OS. It should be limited to use in fit HIR group.

In *PORTEC-1 trial* Creutzberg et al. evaluated 714 patients of HIR stage I disease from1990 to 1997, who were subjected to either observation or percutaneous pelvic radiation with 46 Gy. The primary outcome measure was to assess locoregional recurrence and death, while the secondary outcome measure was to assess

treatment-related morbidity and survival after relapse. The 5-year locoregional recurrence was 14% in the observation group as compared to 4% in the pelvic radiation group. After 15 years also the locoregional recurrence was 15.5% as compared to 6% in the two groups. The study thus concluded that locoregional control is significantly improved by percutaneous pelvic radiation with 46 Gray (Gy) after hysterectomy and bilateral salpingo-oophorectomy in women with unknown lymph node status and an intermediate or high-intermediate risk level. The 5-year overall survival did not show any statistical difference in both the groups (85%in observation versus 81% in radiation). The rates of pelvic recurrence and distant recurrence were not improved by adjuvant radiation. The study recommended limiting adjuvant radiotherapy to patients with age <60 years with G3 and less than half myometrial invasion or any grade with outer half myometrial invasion.

ASTEC/EN.5 trial evaluated 905 patients with intermediate or high-risk early-stage disease from 112 centers in 7 countries from 1996 to 2005. The trial randomly assigned patients to observation or to external beam radiotherapy of 40–60 Gy post surgery. The primary outcome measure was overall survival. 135 women died during the 53 months follow-up and no evidence of survival benefit was observed in the radiotherapy arm, with OS of 85% in both arms.

With the success of cytotoxic chemotherapy in advanced stage endometrial carcinoma, several trials including chemotherapy were initiated to help find the best treatment protocol to tackle the poor prognostic high-risk group. Postoperative treatment with external beam radiation or percutaneous pelvic radiation as proposed in PORTEC-1 trial did not improve the overall survival in these patients. These observations lead to more clinical trials on adjuvant chemotherapy to incorporate this subset of patients. A Cochrane meta-analysis of 9 RCT's which focused on evaluating the effect of chemotherapy in the primary management of early endometrial cancer concluded that postoperative platinum-based trials were associated with a small but definite improvement in PFS and OS irrespective of the radiotherapy [11].

8.4 Clinical Trials Studying Effect of Adjuvant Chemotherapy in Treatment of Women After Surgery and Radiotherapy

1. The first randomized study on adjuvant chemotherapy in endometrial cancer was *GOG-34* [12]. The study population included stages I and II (occult) who after surgery were found to have one or more pathological risk factors such as more than 50% myometrial invasion, cervical involvement, adnexal masses, or pelvic/aortic node metastasis. All patients in this study received adjuvant pelvic external radiotherapy of 50 Gy. Post radiotherapy, these patients were randomized to receive either doxorubicin bolus therapy starting at 60 mg/m^2 up to a maximum of 500 mg/m^2. The investigators found no statistical difference in the survival or progression-free interval. It was concluded that the study was not able to demonstrate the efficacy of doxorubicin on recurrence due to small sample size, number of patients who were lost to follow up, and protocol violations.

To establish optimal treatment, more multicentric trials were conducted.

2. *Japanese Gynaecologic Oncology Group (JGOG 2333)* [13] conducted a multicentric trial that included patients of stage 1C-IIIC disease endometrial carcinoma with more than 50% myometrial invasion. The study compared pelvic radiation therapy (PRT) with cisplatin-based chemotherapy CAP (cisplatin, cyclophosphamide, and doxorubicin). The pelvic radiotherapy group received 40 Gy. The chemotherapy arm received cyclophosphamide 333 mg/m^2, doxorubicin 40 mg/m^2, and cisplatin 50 mg/m^2 every 4 weeks for a minimum of three courses. Both groups showed good compliance. There were no statistical differences in progression-free survival (PFS) (83.5% in radiotherapy versus 81.8% in CAP group) and OS (85.3% in radiotherapy versus 86.7% in CAP group). The study also inferred that in the subset of patients with high- to intermediate-risk group with stage IC in >70 years old with G3 endometrioid adenocarcinoma or stage II/IIIA (positive cytology), the CAP group showed greater PFS (83.8% vs. 66.2%) and higher OS rate (89.7% vs 73.6%). Thus, it was concluded that adjuvant chemotherapy can be a useful option other than radiotherapy in patients of intermediate-risk endometrial cancer.
3. Clinical trials conducted by Maggi et al. [14] in 345 patients of high-risk endometrial carcinoma (stage IC, IIG3 with >50% myometrial space invasion and Stage III) were randomly assigned to adjuvant chemotherapy (CT) with cisplatin 50 mg/m^2, doxorubicin 45 mg/m^2, and cyclophosphamide 600 mg/m^2 every 28 days for 5 cycles or radiotherapy (RT). The follow-up at 3, 5, and 7 years for OS was 78%, 69%, and 62% in the RT group and 76%, 66%, and 62% in the CT group. PFS at 3, 5, and 7 years was 69%, 63%, and 56% in RT group and 68%, 63%, and 60% in CT group. Radiotherapy was seen to delay local responses while chemotherapy delayed metastasis but statistically significant results in this regard could not be achieved. This trial did not show any improvement in survival rates in either CT or RT groups.
4. *The Radiation Therapy Oncology Group (RTOG) 9708 trial* [15] assessed the effect of adjuvant combined chemotherapy along with radiation and radiation alone in grade 2 or 3, Stages IC, IIA, IIB, and III endometrial adenocarcinoma with outer half invasion of the myometrium, cervical stromal invasion, or pelvic-confined extrauterine disease. In the chemoradiation arm, the patients received cisplatin (50 mg/m^2 on day 1 and 28) with radiation followed by 4 cycles of cisplatin (50 mg/m^2) and paclitaxel (175 mg/m^2). The results of this trial showed good locoregional control with 4-year disease-free survival as 85% and as 81%, respectively. Stages IC, IIA, and IIB had no recurrences. The disease-free survival for Stage III patients was 77% and 72%, respectively. The authors concluded that chemoradiation therapy is useful for high-risk, early-stage endometrial carcinoma.
5. *The Nordic Society of Gynecologic Oncology (NSGO)* conducted the *NSGO 9501* [16] and European Organization for Research and Treatment of Cancer *(EORTEC 55991)* [16] conducted a randomized trial on the treatment of early-stage, high-risk endometrial carcinoma with radiotherapy with or without chemotherapy. The phase III trial included patients with stages I–IIIC (positive

peritoneal cytology only) or stage IIIC (positive pelvic lymph nodes) and compared PRT+/−VBT (vaginal brachytherapy) plus cisplatin-based multi-agent chemotherapy (adriamycin + cisplatin, epirubicin + carboplatin, paclitaxel + carboplatin + epirubicin) to only PRT+/−VBT. Completion of therapy was seen in 70% of chemoradiotherapy (CRT) patients and 90% of RT patients. Vaginal brachytherapy was used in 44% of CRT patients and 39% of RT patients. Five year PFS improved to 79% in CRT patients and 72% RT patients. The RT alone patients had a higher chance of relapsing outside the pelvis—16% as compared to 10% CT. The author concluded that combined chemotherapy and radiation is superior to radiation alone as adjuvant therapy for early endometrial cancer with high-risk features for metastasis.

6. *MaNGO ILIADe III Trial* [17]—Mario Negri Gynecologic Oncology group, an Italian collaborative made a comparison of survival rates in 157 women endometrioid adenocarcinoma who were randomly assigned into two groups. The first group did not receive any additional treatment other than surgery followed by radiotherapy and the second group was treated with doxorubicin 60 mg/m^2 plus cisplatin 50 mg/m^2 every 3 cycles after surgery but before radiotherapy. The combined treatment resulted in 36% reduction in risk of relapse, a significantly better disease-free survival (HR, 0.55; 95% CI, 0.35–0.88; $p = 0.01$) and near significant improvement in overall survival (HR, 0.55; 95% CI, 0.46–1.03; $p = 0.07$).

   In NSGO/EORTC study after amendment, chemotherapy could be administered either before or after the radiotherapy and consisted of four courses. While in the Italian MaNGO ILIADe III trial chemotherapy was given prior to radiotherapy. In the pooled analysis of the above three trials, the risk of relapse or death was similar but with a narrower confidence interval. Neither study showed a significant difference in overall survival.

   The two studies conducted by JGOG 2033 and EORTEC 55991 had a limitation that they had both patients of high-risk, early-stage disease generalized with surgically inoperable and incompletely inoperable advanced stage patients in the same group. Even though they demonstrated an improvement in overall survival (OS) in the higher risk group but the proportion of this subset of patients in the study was only 25–40%, therefore more clinical trials were required.
7. *Kuoppala 2008* [18]—It was a multi-institutional randomized Finish trial that evaluated the effect of Sandwich regimen with three courses of chemotherapy cisplatin 50 mg/m^2, epirubicin 60 mg/m^2, and cyclophosphamide 500 mg/m^2 given once after surgery than in between two radiotherapy cycles and on after the chemotherapy cycle. 156 patients with Stage IA-B grade 3 or stage IC–IIIA grade 1–3 were randomized postoperatively to two arms of RT and CRT. The 5-year survival in RT was 84.7% and 82.1% in CRT group. The chemotherapy group was associated with tolerable acute toxicity. The investigators concluded that adjuvant chemotherapy failed to improve survival or lower the recurrence rate in patients with high-risk endometrial carcinoma.
8. In the study *GOG 249* [19], by Randall et al. from 2009 to 2013, published in 2019, a population of high-risk, early-stage endometrial cancer patients were identified who may benefit from aggressive adjuvant therapy. A comparison was done between vaginal cuff brachytherapy combined with chemotherapy (carbo-

platin and paclitaxel) to pelvic radiation alone. After a median follow-up of 53 months, they inferred that chemoradiation did not improve progression-free survival (PFS). An increased incidence of adverse effects was seen in patients receiving chemotherapy. There were no differences in vaginal or distant failure rates. Pelvic and para-aortic nodal failures were more common among patients who received vaginal cuff brachytherapy with chemotherapy. A subset analysis of patients with serous or clear cell tumors did not find a benefit in PFS or OS with vaginal cuff brachytherapy combined with chemotherapy.

9. The *PORTEC 3 trial* [20] conducted by de Boer SM et al. from 2006 to 2014 and published in 2018, included 660 high-risk, early-stage endometrioid endometrial cancers (stage I grade 3 endometrioid cancers with deep myometrial invasion or LVSI, stage IB, stages II and III endometrioid cancers, serous, and clear cell carcinoma). This clinical trial compared two management protocols of chemoradiation and whole pelvic radiation. The patients received either teletherapy of 48.6 Gy only or were given cisplatin (50 mg/m^2) twice in addition, in the first and fourth weeks of radiation, followed by 4 cycles of carboplatin (AUC5) and paclitaxel (175 mg/m^2). The average follow-up period was 60.2 months. The primary co-endpoints for the study were failure-free survival (FFS) which was defined as recurrence or death due to EC or therapy, and overall survival.

The 5-year overall survival rate was 81.8% with chemoradiotherapy as compared to 76.7% with radiotherapy alone. The 5-year FFS was significantly better in the chemoradiotherapy group than in the group which had radiotherapy alone (75.5% vs. 68.6%), but this difference was not statistically significant. The effects of chemoradiotherapy were seen most clearly in patients with FIGO stage III (increase in the 5-year overall survival from 69.8 to 78.7%). No statistically significant difference was found in the small subgroup of patients with serous carcinoma (5-year FFS of 58% after chemoradiotherapy and 48% after radiotherapy). The incidence of side effects occurred in 60% of patients with chemoradiotherapy compared with only 12% of patients who had radiotherapy alone ($p < 0.0001$). Persistent neuropathies (≥grade 2) were observed after 3 years in 8% of women after chemoradiotherapy compared with only 1% after radiotherapy ($p < 0.0001$).

The study inferred that chemoradiotherapy cannot be recommended as the new standard for patients with high-risk EC in FIGO stages I and II. However, this therapy can be discussed with patients in stage III, but keeping in mind the toxicity associated with it. The study inferred no significant improvement in failure-free survival (FFS) or OS to justify the addition of chemotherapy in stage I or II endometrioid cancers. Therefore, this trial also recommends against chemotherapy for high-risk stages I and II endometrioid endometrial cancers.

The clinical trials conducted till now have not been able to demonstrate any additional benefit of chemotherapy in early-stage disease even with the presence of high risk. As recommended by various PORTEC trials [7, 20, 21] patients with grade 3 endometrioid cancer with deep myometrial invasion or LVSI or both should be offered external beam radiation. The other high-risk patients may be treated with adjuvant vaginal cuff brachytherapy (Table 8.1).

Table 8.1 Clinical trials of adjuvant chemotherapy in early-stage disease

Trial	Eligibility	Arms	Outcome	Conclusion
GOG-34	Stage I or II (occult) with • More than 50% myometrial invasion • Cervical involvement • Adnexal masses • Pelvic/ aortic node metastasis	1. Observation = 91 2. Doxorubicin bolus therapy (60 mg/m^2 up to a maximum of 500 mg/ m^2), *N* = 89	5-year survival rate in patients with deep myometrial invasion, cervical involvement and pelvic lymph node metastasis were similar in both groups 63–70% 5-year survival in patients with aortic node metastasis was 26%	The study was not able to demonstrate the efficacy of doxorubicin on recurrence due to small sample size, number of patients who were lost to follow-up and protocol violations
JGOG 2333	Stage 1C-IIIC with > than 50% myometrial invasion	• Pelvic radiation therapy (PRT), *N* = 193 • Cisplatin-based chemotherapy CAP (cisplatin, cyclophosphamide, and doxorubicin), *N* = 192	No statistical difference in PFS-83.5% in RT vs 81.8% in CT No statistical difference in OS 85.3% in RT vs 86.7% in CT High- to intermediate-risk with stage IC in >70-year old with G3 endometrioid adenocarcinoma or stage II/ IIIA (positive cytology), CT group greater PFS—(83.8% vs 66.2%) and higher OS rate (89.7% versus 73.6%)	It concluded that adjuvant chemotherapy can be a useful option other than radiotherapy in patients of intermediate risk endometrial cancer
Maggi et al.	Stage IC, stage IIG3 with >50% myometrial space invasion Stage III	• Chemotherapy (CT) with cisplatin, doxorubicin, and cyclophosphamide, *N* = 174 • Pelvic radiotherapy (RT) +/− para-aortic RT *N* = 166	Follow-up OS at 3, 5, and 7 years was 78%, 69%, and 62% in the RT group and 76%, 66%, and 62% in the CT group Follow-up PFS at 3, 5, and 7 years was 69%, 63%, and 56% in RT group and 68%, 63%, and 60% in CT group	This trial did not show any improvement in survival rates in either CT or RT groups
RTOG 9708 trial	Stage IC, IIA, and IIB grade 2 or 3 endometrial adenocarcinoma with outer half invasion of the myometrium, cervical stromal invasion, or pelvic-confined extrauterine disease	• Chemoradiation with Cisplatin, D1, and D28 with radiation followed by 4 cycles cisplatin and paclitaxel • Radiation alone	4-year disease-free survival as 85% and as 81%, respectively Stage IC, IIA, and IIB had no recurrences The disease-free survival for stage III patients was 77% and 72%, respectively	The results of this trial showed good locoregional control The authors concluded that chemoradiation therapy is useful for high-risk, early-stage EC

NSOG-EC-9501 in collaboration with EORTC -55,991 *N* = 320	Stage I, stage II, IIIA (positive peritoneal cytology), or IIIC (positive pelvic Lymph nodes) Risk factor—grade3 with >50% myometrial infiltration, serous, clear cell, anaplastic ca, endometrial ca confined to cervix, regional lymph nodes, or positive peritoneal cytology	• PRT+/− VBT (vaginal brachytherapy) plus cisplatin-based multi-agent chemotherapy (adriamycin + cisplatin, epirubicin + carboplatin, paclitaxel + carboplatin + epirubicin) • PRT+/−VBT	Completion of therapy was seen in 70% of CRT patients and 90% of RT patients. Vaginal brachytherapy was used in 44% of CRT patients and 39% of RT patients. 5-year PFS improved to 79% in CRT patients and 72% RT patients. The RT alone patients had a higher chance of relapsing outside the pelvis—16% as compared to 10% CT	The author concluded that combined chemotherapy and radiation is superior to radiation alone as adjuvant therapy for early endometrial cancer with high-risk features for metastasis
MaNGO ILIADE-3 *N* = 157	Stage I, stage II, IIIA (positive peritoneal cytology) or IIIC (positive pelvic lymph nodes) Risk factor—grade3 with >50% myometrial infiltration, serous, clear cell, anaplastic ca, endometrial ca confined to cervix, regional lymph nodes or positive peritoneal cytology	• Pelvic radiation • CT prior to radiotherapy (doxorubicin 60 mg/m^2 plus cisplatin 50 mg/m^2 every 3 cycles after surgery but before radiotherapy)	The combined treatment resulted in 36% reduction in risk of relapse, a significantly better disease-free survival (HR, 0.55; 95% CI, 0.35–0.88; $p = 0.01$) and near significant improvement in overall survival (HR, 0.55; 95% CI, 0.46–1.03; $p = 0.07$)	The author compiled data with NSOG–EC 9501 & EORTC 55991 trial and gave a similar conclusion
Kuoppala et al.	Stage IA-B/grade 3 Stage IC Stage IIIA	• Pelvic radiation, cisplatin/epirubicin/ cyclophosphamide, *N* = 84 • Pelvic radiation, *N* = 72	5-year PFS—74.4%in CRT vs 82% in RT 5-year OS 82.1% in CRT vs 84.7% in RT	The investigators concluded that adjuvant chemotherapy failed to improve survival or lower the recurrence rate in patients with high-risk endometrial carcinoma

(continued)

Table 8.1 (continued)

Trial	Eligibility	Arms	Outcome	Conclusion
GOG 249 [14], by Randall et al.	Stage I with HIR criteria Stage II Stage I–II serous/clear cell (CC) with negative washings	• Pelvic RT • Vaginal cuff Brachytherapy (VCB) followed by carboplatin AUC6/ paclitaxel 175 mg/m^2 21 days × 3 cycles	60 month RFS—0.76 RT vs 0.76 VCB/C 60 month OS 0.87 RT vs 0.85 VCB/C 5 year vaginal recurrence 2.5% vs 2.5% 5-year distant recurrence 18% vs 18%	VCB/C did not improve recurrence-free survival or OS with RT In serous and CC VCB/C did not improve RFS or OS Pelvic/para-aortic nodal failures more common in VBC/C Pelvic RT preferred in high-risk early EC
PORTEC 3 trial *N* = 660	Stage IA G3 with LSVI Stage IB G3 Stage II Stage III Stage I-III S or CC	• Pelvic RT teletherapy of 48.6 Gy • Combination CT and RT cisplatin (50 mg/m^2) week 1 and 4 of RT followed by carboplatin (AUC5) and paclitaxel (175 mg/m^2). Q3 weeks × 4 cycles	5-year OS 81.8% CTRT vs 76.7% RT 5-year FFS 75.5% CTRT vs 68.8% RT >G3 adverse effect 60% CTRT vs 12% RT Subgroup—Stage III 5-year FFS 69.3% CTRT vs 58% RT 5-year OS 78.7% CTRT vs 69.8% RT	CTRT did not improve OS although it did not increase FFS Subgroup analysis of stage III improved 5-year FFS and trend toward OS

8.5 Advanced Endometrioid Endometrial Cancers (Stages III and IV)

In cases of stage III or IV endometrial cancer the recommended management protocol is:

1. Surgically Resected: Offer chemotherapy with the addition of radiation therapy in appropriate cases (CT + RT).
2. Unresectable: Largely treated with chemotherapy; the role of radiotherapy should be individualized.

Limitations in conducting trials in advanced-stage disease are number of patients and the follow-up time available. Formulation of postoperative adjuvant treatment for advanced endometrial cancer is also challenging, as in patients who receive chemotherapy alone are at an increased risk of pelvic failure while those who receive radiation alone are at increased risk of distant failure.

GOG122 [22] trial compared whole-abdominal radiotherapy (WART) versus systemic chemotherapy (eight cycles of doxorubicin and cisplatin) in 388 patients with stage III or IV disease of any histology who underwent surgical resection with residual disease less than 2 cm. Radiotherapy involved 30 Gy per day to the whole abdomen with a 15 Gy boost to the pelvis. Chemotherapy included doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 every 3 weeks for seven cycles. The results of this study showed a significant advantage of chemotherapy on 5-year survival. Patients who received chemotherapy had a 13% improvement in 2-year progression-free survival (50% vs. 46%) compared with patients treated with whole-abdomen radiation. An 11% improvement in overall 2-year survival (70% vs. 59%) compared with patients treated with whole-abdomen radiation. The drawback of this trial was that it included post-surgery residual tumors up to 2 cm for which the radiotherapy dose was insufficient.

GICOG [23]—This Italian trial considered 345 women of stage IC Grade 3, stage II grade 3 with myometrial invasion >50% and stage III. They randomly assigned groups of RT with 50 Gy external beam to pelvis on a 5-day week schedule to 45 fractions and chemotherapy groups. In chemotherapy 5 cycles of cisplatin 50 mg/m^2, doxorubicin 45 mg/m^2, and cyclophosphamide 600 mg/m^2 every 28 days. The study concluded an improvement in overall and progression-free interval after 3, 5, and 7 years.

GOG 258 [24] trials conducted from 2009 to 2014, included patients with stage III–IVA disease with less than 2 cm of residual disease. It compared chemoradiation (Cisplatin 50 mg/m^2 D1& D29 plus volume directed RT) followed by four cycles of paclitaxel/carboplatin (paclitaxel 175 mg/m^2 and carboplatin AUC5 Q21 days) to six cycles of paclitaxel/carboplatin alone. They found vaginal recurrence of 3% in the chemoradiation (CRT) group as compared to 7% in the chemotherapy (CT) group. The pelvic and para-aortic recurrences were 10% in CRT group as compared

to 21% in the CT group. There was no improvement in PFS or OS with CRT. More acute toxicities were experienced in CRT and distant recurrences were more common in CRT.

PORTEC 3 trial [20] that has been discussed included patients with high-risk stage I–III endometrial cancer. The results of these phase 3 trials were not definite to suggest the best option for adjuvant therapy for advanced disease but may the benefit of adjuvant chemotherapy in stage III disease may be considered as a treatment option, keeping in mind the high toxicity associated with chemotherapeutic agents.

The National Comprehensive Cancer Network (NCCN) [25] recommendations for adjuvant therapy of advanced-stage endometrial cancers are systemic therapy with or without vaginal brachytherapy or EBRT with or without vaginal brachytherapy with or without systemic therapy.

Clinical data, therefore, suggests that adjuvant chemotherapy has a role in management of stage III and IV disease (Table 8.2).

8.6 Serous and Clear Cell Endometrial Cancers

Both serous and clear cell endometrial carcinomas are less common but more aggressive types. They differ in their molecular profiles than type 1 endometrioid histologies. Serous carcinomas account for 3–10% of endometrial cancers but are responsible for 39% of deaths due to endometrial cancer [4]. 90% of these are known to have TP53 alterations and 30% have HER2/neu alterations [26]. They are notorious for having extrauterine spread at the time of presentation. Clear type carcinomas account for 4% of all uterine tumors and present with occult metastasis in 40% of the cases [27]. About 30–40% have TP53 alterations, 15% have microsatellite instability (MSI) and 30% have phosphatase and tensin homolog (PTEN) alterations [26].

Various clinical trials conducted till now have included patients of serous and clear cell carcinomas in their study groups. The trail of *GOG 249* [19] included patients with stage I or II serous and clear cell uterine cancer with negative cytology while *GOG 258* [24] included stage I or II with positive cytology and stage III or IV. The *PORTEC 3* trial [18] also included patients with stages I to III serous or clear cell cancers. The limitations of the above trials are that this subset of patients accounts for only 20% of the study population, therefore, it is difficult to draw conclusions from the study results for this subset of patients.

The *NCCN guidelines* recommend chemotherapy with or without vaginal brachytherapy for IA serous or clear cell endometrial cancers, although they offer observation or EBRT as acceptable alternatives. For IB (or greater) disease, they recommend chemotherapy with or without EBRT with or without vaginal brachytherapy [25].

Adjuvant chemotherapy is recommended for uterine serous and clear cell carcinomas with any myometrial invasion due to their aggressive nature to metastasize.

Table 8.2 Chemotherapy in advanced endometrial cancer

Trial	Eligibility	Arms	Outcome	Conclusion
GOG 122	III/IV (post-residual disease < 2 cm)	• WART (30 Gy in 20 fx with 15 Gy boost • CT- doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 Q3× 7 cycles, followed by 1 cycle of cisplatin	Local recurrence 13% in WART vs 18% in AP Distant recurrence 38% in WART vs 32% in AP	Chemotherapy improved PFS and OS compared with WART
GICOG *N* = 345	Stage IC grade 3, stage II grade 3 with myometrial invasion >50% and stage III	• CT- 5 cycles of cisplatin 50 mg/m^2, doxorubicin 45 mg/m^2 and cyclophosphamide 600 mg/m^2 every 28 days • RT (50 Gy external beam to pelvis on a 5 day week schedule to 45 fractions)	3, 5, 7 year OS were 76%, 66%, and 62% ass with CT vs 78%, 69% and 62% after RT 3, 5, 7 year PFS were 68%, 63%, and 60% in CT vs 69%, 63%, and 56% in RT	The study concluded an improvement in overall and progression-free interval after 3, 5, and 7 years
GOG 258	Stage III–IVA disease with less than 2-cm residual disease I–II serous/CC with positive washings	• Cisplatin 50 mg/m^2 intravenous D1 and D29+ volume directed RT followed by carboplatinAUC5/paclitaxel 175 mg/m^2 Q21 days × 4 cycles with G-CSF support • Carboplatin AUC 6/paclitaxel 175 mg/m^2 Q21 × 6 cycles	Vaginal recurrence 3% in CRT vs 7% CT Pelvic and Para-aortic recurrence—10% CRT vs 21% CT Distant recurrences—28% CRT vs 21% CT 6-year recurrence-free survival 35.7% CRT vs 38.95% CT >G 3 toxicity 58% CRT vs 63% CT	Chemoradiation did not improve RFS compared to RT More acute toxicities in CRT vs RT Less vaginal, pelvic and para-aortic failures in CRT Distant recurrences more common in CRT than CT
PORTEC 3 trial *N* = 660	Stage IA G3 with LSVI Stage IB G3 Stage II Stage III Stage I-III S or CC	• Pelvic RT teletherapy of 48.6 Gy • Combination CT and RT cisplatin (50 mg/m) week 1 and 4 of RT followed by carboplatin (AUC5) and paclitaxel (175 mg/m). Q3 weeks × 4 cycles	5 year OS 81.8% CTRT vs 76.7% RT 5 year FFS 75.5% CTRT vs 68.8% RT >G3 adverse effect 60% CTRT vs 12% RT Subgroup—Stage III 5-year FFS 69.3% CTRT vs 58% RT 5 year OS 78.7% CTRT vs 69.8% RT	CTRT did not improve OS although it did not increase FFS Subgroup analysis of stage III improved 5-year FFS and trend toward OS

HER2/neu: Positive Serous Endometrial Tumors
Fader et al. [28] published their randomized phase II trial of paclitaxel and carboplatin with or without trastuzumab in primary stage III or IV or recurrent HER2/neu-positive uterine serous carcinomas. They randomly assigned 61 patients and found a median PFS of 12.6 months in the paclitaxel, carboplatin, and trastuzumab arm versus 8.0 months in the paclitaxel and carboplatin alone arm. In the 41 patients with primary advanced-stage disease, the PFS was 17.9 months in the trastuzumab arm versus 9.3 months in the paclitaxel/carboplatin alone arm. In the 17 patients with recurrent disease, PFS was 9.2 months in the trastuzumab arm versus 6 months in the paclitaxel/carboplatin arm. The overall survival benefit in Trastuzumab group in these preliminary results raises hopes of guiding management with HER2/neu tumor profiling which in the coming years will lay down rules for targeted therapy.

8.7 Current S3 Guidelines Based on Clinical Trials Related to Adjuvant Chemotherapy

The current S3 guideline "Diagnosis, treatment and follow-up of patients with endometrial cancer" [29] recommends the following procedures:

- Adjuvant chemotherapy can be given to patients with type II EC and to patients with type I EC G3, pT1b, and stage pT2 (all pN0) (Level of Evidence [LoE] 2).
- Patients with EC stage pT3 and/or pN1 should receive adjuvant chemotherapy (LoE1).
- Patients with EC stage pT4a who were macroscopically tumor-free after surgery or have a maximum residual tumor under 2 cm should receive chemotherapy (LoE1).

8.8 Therapy for Recurrent or Metastatic Disease

The initial therapy for unresectable recurrent/metastatic disease is chemotherapy with carboplatin and paclitaxel. For those with potentially endocrine-sensitive tumors, progestin-based therapies have also been tried.

Trials have shown that combination chemotherapy has resulted in higher response rates than single-agent therapy. *GOG trial 107* [30] for stages III, IV, or recurrent disease combination of doxorubicin with cisplatin against doxorubicin alone to assess response rate and progression-free survival. The overall response rate was higher among patients with combination therapy (42% vs 25%). The median PFS was 5.7% and 3.8%, respectively, in the two groups. Combination therapy was associated with increased toxicity.

EORTC-55872 [31] trials also compared the above regimens and reported similar results.

GOG 177 Trial [32], conducted by Flemming et al., compared doxorubicin 60 mg/m^2 and cisplatin 50 mg/m^2 to doxorubicin 45 mg/m^2 and cisplatin 50 mg/m^2 on day 1 followed by paclitaxel 160 mg/m^2 on day 2 with filgrastim. The three drug regimen resulted in superior response rate, PFS and OS. Higher neurological toxicity was noted in this group.

GOG 209 Trial [33] conducted by Miller et al. was completed in 2009, compared paclitaxel and carboplatin (CT) to doxorubicin, cisplatin, and paclitaxel (TAP) in patients with advanced-stage or recurrent cancer. No difference in the two groups was noted in terms of treatment options as reported in the interim analysis. The median PFS was 14 months in both the groups, whereas median OS was 32 and 38 months, respectively. The two drug regimen was better tolerated, especially in terms of neuropathy. The study had to be discontinued in 18% of patients with TAP and in 12% patients with CT due to toxicities.

These trials concluded that though cisplatin, paclitaxel; carboplatin, paclitaxel; and doxorubicin, cisplatin, and paclitaxel are actively used combination drugs in advanced and recurrent cancers, the acceptability of carboplatin and paclitaxel is more as it is better tolerated.

Ongoing Trials for Recurrent disease:

- PORTEC—4a trial phase 3 Molecular Profile based Versus standard Adjuvant Radiotherapy in Endometrial Cancer. NCT03469674
- Phase 2 trial of Cobozantinib S—Maleate in treating patients of recurrent or metastatic endometrial cancer. NCT01935934
- Phase 2 of paclitaxel, carboplatin, and pemburozumab in measurable advanced or recurrent endometrial cancer. NCT02549209
- Phase 2 trial of vaginal cuff brachytherapy followed by adjuvant chemotherapy with carboplatin and dose-dense paclitaxel in patients with high-risk endometrial cancer. NCT03189446
- Phase 2 trial comparing single-agent olaparib, single-agent cedirinib, or combination cedirinib/olaparib in women with recurrent, persistent, or metastatic endometrial cancer. NCT03660826

8.9 Conclusion

The data on adjuvant therapy of endometrial cancer are inconsistent. Recent trials have investigated the value of adjuvant radiotherapy, chemotherapy, and combined adjuvant combined chemoradiotherapy with varying results. It is important to individualize treatment and discuss the options available with the patient taking into account the benefits and disadvantages of chemotherapy and radiotherapy. Translational research is ongoing to further characterize individual tumors, identify sensitivity to hormonal and immunotherapies, and find new treatment targets to improve outcomes.

8.10 Key Points

1. Globally endometrial cancer accounts for 5.3% of cancers affecting women.
2. Advanced-stage and some high–risk, early-stage endometrial cancers are at increased risk of developing micrometastatic disease and recurrence. Clinical trials are evaluating adjuvant treatment options in this subset of patients.
3. The clinical trials conducted till now have not been able to demonstrate any additional benefits of chemotherapy in early-stage disease even with the presence of high risk.
4. Cochrane meta-analysis of 9 RCT's which evaluated the effect of chemotherapy in the primary management of early endometrial cancer concluded that postoperative platinum-based trials were associated with a small but definite improvement in PFS and OS irrespective of the radiotherapy.
5. Clinical data suggest that adjuvant systemic chemotherapy has a role in the management of stages III and IV disease with or without vaginal brachytherapy.
6. Adjuvant chemotherapy is recommended for uterine serous and clear cell carcinomas with myometrial invasion due to their aggressive nature to metastasize.
7. In advanced and recurrent cancers, carboplatin, and paclitaxel are better tolerated and accepted than other combination chemotherapeutic options.

References

1. UCSF clinical trials: how clinical trials work. https://clinicaltrials.ucsf.edu/about/how-clinical-trials-work
2. Worldwide cancer data/World cancer research fund. http://www.wcrf.org > diet and cancer.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34.
4. Hamilton CA, Cheung MK, Osann K, et al. Uterine papillary serous and clear cell carcinomas predict poorer survival compared to grade 3 endometrioid corpus cancers. Br J Cancer. 2006;94(5):642–6.
5. Evans T, Sany O, Pearmain P, et al. Differential trends in the rising incidence of endometrial cancer by type: data from a UK population-based registry from 1994 to 2006. Br J Cancer. 2011;104(9):1505–10.
6. Keys HM, Roberts JA, Brunetto VL, 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. Creutzberg CL, van Putten WL, Kopper PC, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage I endometrial carcinoma: multicentre randomised trial. PORTEC study group. Post operative radiation therapy in endometrial carcinoma. Lancet. 2000;355:1404–11.
8. Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer. A gynecologic oncology group study. Cancer. 1987;60(Suppl 8):2035–41.
9. Humber C, Tierney J, Symonds P, et al. Chemotherapy for advanced, recurrent or metastatic endometrial carcinoma. Cochrane Database Syst Rev. 2005;3:CD003915.
10. Blake P, Swart AM, Orton J, ASTEC/EN. 5 Study Group, et al. Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MR ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systemic review, and meta analysis. Lancet. 2009;373:137–46.

11. Johnson N, Bryant A, Cornes P, et al. Adjuvant chemotherapy for endometrial cancer after hysterectomy. Cochrane Database Syst Rev. 2011;10:CD003175.
12. Morrow CP, Bundy BN, Homesly HD, et al. Doxorubicin as adjuvant following surgery and radiation therapy in patients with high risk endometrial cancer, stage I and occult stage II: a gynecologic oncology group study. Gynecol Oncol. 1990;36:166–71.
13. 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.
14. 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.
15. Gravin K, Winter K, Underhill K, et al. Final analysis of RTOG 9708: adjuvant postoperative irradiation combined with cisplatin paclitaxel chemotherapy following surgery for patients with high risk endometrial cancer. Gynecol Oncol. 2006;103(1):155–9.
16. Hogberg T, Rosenberg P, Kristensen G, de Oliveira CF, et al. A randomised phase III study on adjuvant treatment with radiation (RT) +/− chemotherapy (CT) in early stage high risk endometrial cancer (NSOG – EC – 9501/EORTC 55991). J Clin Oncol. 2007;25(18S):5503.
17. Hogberg T, Signorelli M, de Oliveria CF, et al. Sequential adjuvant chemotherapy and radiotherapy in endometrial cancer—results from two randomised studies. Eur J Cancer. 2010;46:2422–31.
18. Kuoppala T, Maenpaa J, Tomas E, et al. Surgically staged high- risk endometrial cancer: randomized study of adjuvant radiotherapy alone vs sequential radiotherapy. Gynecol Oncol. 2008;110(2):190–5.
19. Randall ME, Filiaci V, McMeekin DS, et al. Phase III trial: adjuvant pelvic radiation therapy versus vaginal brachytherapy plus paclitaxel/carboplatin in high-intermediate and high-risk early stage endometrial cancer. J Clin Oncol. 2019;37:1810. https://doi.org/10.1200/JCO.18.01575.
20. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19(3):295–309.
21. Nout RA, Smit VT, Putter H, 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;375:816–23.
22. Brunner DW, Barsevick A, Tian C, et al. Randomized trial of quality of life comparing whole abdomen irradiation versus combination chemotherapy in advanced endometrial carcinoma: a gynecologic oncology group study. Qual Life Res Int J Qual Life Asp Treat Care Rehab. 2007;16(1):89–100.
23. Maggi R, Cagnazzo G, Atlante G, et al. Risk groups and adjuvant therapy in surgical staged endometrial cancer patients. A randomized multicentre study comparing chemotherapy with radiation therapy. Int J Gynecol Cancer. 1999;(suppl 1):85.
24. Matei D, Filiaci VL, Randall M, et al. A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma. J Clin Oncol. 2017;35:5505.
25. Wui-Jin KM, Abu-Rustum NM, Bradley KM: National Comprehensive Cancer Network. Uterine Neoplasms (Version 1.2019). Accessed November 22, 2018. Reference Source [Google Scholar].
26. Buhtoiarova TN, Brenner CA, Singh M. Endometrial carcinoma: role of current and emerging biomarkers in resolving persistent clinical dilemmas. Am J Clin Pathol. 2016;145(1):8–21.
27. Carcanglu ML, Chambers JT. Early pathologic stage clear cell carcinoma and uterine papillary serous carcinoma of the endometrium: comparison of clinicopathological features and survival. Int J Gynecol Pathol. 1996;14(1):30–8.
28. Fader AN, Roque DM, Siegel E, et al. Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. J Clin Oncol. 2018;36(20):2044–51.

29. Statement of the Uterus Committee of the Gynaecological Oncology Working Group (AGO) on the PORTEC-3 study. Geburtshilfe Frauenheilkd. 2018 Oct;78(10):923–6.
30. Thigpen JT, Brady MF, Homesley HD, et al. Phase III trial of doxorubicin with or without cisplatin in advanced endometrial carcinoma: a gynaecologic oncology group study. J Clin Oncol. 2004;22:3902–8.
31. Van Wijk FH, Aapro MS, Bolis G, et al. European organization for research and treatment of cancer gynaecological cancer group. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by EORTC gynaecological cancer group. Ann Oncol. 2003;14:441–8.
32. Flemming GF, Filiaci VI, Bentley RC, et al. Phase III randomised trial of doxorubicin + cisplatin versus doxorubicin + 24 h paclitaxel + filgastrim in endometrial carcinoma: a gynecological oncology group study. Ann Oncol. 2004;15:1173–8.
33. Miller D, Filiaci V, Fleming G, et al. Breaking abstract I: randomised phase III non-inferiority trial of first line chemotherapy for recurrent endometrial carcinoma: a gynecological oncology group study. Gynecol Oncol. 2012;125:771.

Adjuvant Radiation Therapy in Carcinoma Endometrium: An Update

9

Kanika Sharma Sood

Radiation therapy (RT) has been employed for the treatment of endometrial cancer for many decades. The radiation delivery techniques have changed leaps and bounds in the last 2 decades, so have the indications of adjuvant radiation therapy. With newer diagnostic tools, a better understanding of disease biology, availability of long-term data on outcomes of treatment, the risk criteria have been redefined in the last 3 years.

Decisions about adjuvant therapy for endometrial carcinoma are based upon clinicopathologic risk factors. Following surgical staging, there are certain factors that predict the risk of relapse and persistent disease. Nowadays in a diagnosed endometrial cancer, treatment is stratified based on the risk of disease recurrence which takes into account the stage of disease, histology of the tumor, and other pathologic factors. Still, there are many ambiguities and the treatment is not clearly spelled out despite multiple trials. This can be attributed to inadequate power in many studies due to heterogeneity in patient selection criteria, low recurrence rates in early-stage endometrial cancer, and competing for risk of death from other causes in women with endometrial cancer.

Most radiation oncology bodies including ASTRO and ESTRO define the adjuvant treatment based on these risk stratifications [1].

9.1 Risk Stratification of Endometrial Cancers

The women with carcinoma endometrium can be stratified into three risk subgroups—Low risk, Intermediate risk, and high risk (Table 9.1) [2].

Low-risk endometrial cancer includes grade 1 endometrial cancer of endometrioid histology that is confined to the endometrium (a subset of stage IA disease).

K. S. Sood (✉)
Radiation Oncology, Dharamshila Narayana Superspeciality Hospital, New Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_9

Table 9.1 Risk stratification

Risk group	Description
Low	Stage I endometrioid, grade 1–2, <50% myometrial invasion, LVSI negative
Intermediate	Stage I endometrioid, grade 1–2, ≥50% myometrial invasion, LVSI negative
High-intermediate	Stage I endometrioid, grade 3, <50% myometrial invasion, regardless of LVSI status Stage I endometrioid, grade 1–2, LVSI II unequivocally positive, regardless of depth of invasion
High	Stage I endometrioid, grade 3, ≥50% myometrial invasion, regardless of LVSI status, Stage II, Stage III endometrioid, no residual disease, Non-endometrioid (serous or clear cell or undifferentiated carcinoma or carcinosarcoma)
Advanced	Stage III residual disease and stage IV A
Metastatic	Stage IV B

The overall probability of recurrence in these groups is very low following surgical treatment alone.

Intermediate-risk endometrial cancer includes women with uterine-limited cancer that invades the myometrium (stage IA or IB) or has occult cervical stromal invasion (stage II). These groups have a higher risk of recurrence and require adjuvant therapy. The group is further stratified into high- and low-intermediate risk by evaluation of adverse prognostic factors like outer one-third myometrial invasion, grade 2 or 3 differentiation, or the presence of lymphovascular invasion.

High-risk endometrial cancer includes stage III or higher endometrial cancer, regardless of histology or grade. However, women with a serous (USC) or clear cell (CC) carcinoma are deemed at high risk irrespective of stage. Due to high risk of relapse and death, this subgroup multimodality adjuvant therapy is required.

There are several other prognostic factors that were previously considered when a decision regarding adjuvant radiation therapy was taken. These include:

Older Age Whether age represents an independent prognostic factor is controversial. It has been associated with higher rates of clinical failure and survival in some studies including the Gynaecologic Oncology Group (GOG) protocol 33 which estimated the 5-year survivals in stage I and II disease. There was a significant decrease in survival rate which were up to 94% in patients aged 41–50 years and fell down to 54% in patients aged more than 80 years [3–6]. But several other studies could not confirm this age relationship in survival outcome [7].

Women more than 65 years old tend to have high tumor grade tumors with deep myometrial invasion and advanced stage. Additionally, the inability to deliver aggressive therapy in old age contributes toward poorer survivals in this age group. Age is still used to categorize women with intermediate-risk disease into either a high or a low-intermediate risk group.

Lower Uterine Segment Involvement It was known to harbor a greater risk for nodal involvement. However, it is not clear if involvement of the lower uterine seg-

ment represents an independent risk factor for survival. Hence, it is now excluded from the risk stratification criteria.

Positive peritoneal cytology which was appreciated in up to 11% of patients is no longer considered in the staging system for endometrial carcinoma [8]. This is due to the fact that prognostic significance of isolated positive peritoneal washings in the absence of extra-uterine spread remains controversial [9, 10]. Hence peritoneal cytology results are not taken into account during the formulation of a treatment plan for patients with endometrial cancer.

Newer Markers Some more Molecular prognostic factors are being extensively explored in studies to establish their prognostic value. These include p53 and p16 overexpression, phosphatase and tensin homolog (PTEN) mutations, markers of proliferation, microsatellite instability, tumor expression of estrogen (ER), and/or progesterone (PR) receptors, or proteins involved in the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mechanistic target of rapamycin (mTOR) pathway. POLE mutations also help in risk stratification, the POLE mutated cancers even if grade 3 have a lower risk of recurrence. Currently, they are investigational and hold promise for the future in predicting outcome and defining treatment for carcinoma endometrium patients [11, 12].

9.2 Radiation Therapy for Carcinoma Endometrium

Before proceeding to understand the risk model based adjuvant radiation therapy it is pertinent to understand the different modes of delivery of radiation therapy. The radiation therapy can be delivered by two means—either external beam radiation therapy or brachytherapy.

9.2.1 External Beam Radiation Therapy

It delivers high-energy photons to the entire pelvis including all the regional lymph nodes (obturator and iliac lymph nodes). Conventional planning and delivery techniques used four field techniques covering the vaginal cuff and all locoregional draining lymphatics. In the conventional techniques, the area to be treated was identified by bony landmarks based on 2D anatomy as determined by planning radiographs (called simulation films) [13]. The dose received by the rectum and bladder in this situation cannot be individually determined but is usually similar to those received by vaginal cuff and nodal regions. This contributes to higher toxicity to these organs, especially bowel toxicity as in the postoperative case, the small bowel falls into the pelvis due to space created by hysterectomy (Fig. 9.1).

Modern radiation therapy machines like linear accelerators deliver more conformal therapy where the target area which has to be treated is delineated on a CT scan image and dose computation is done by computerized algorithms. More conformal techniques include Intensity Modulated radiation therapy (IMRT) where radiation

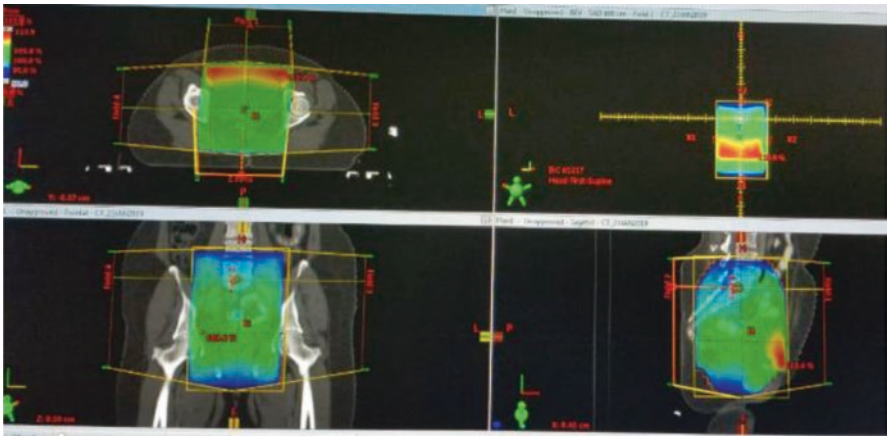


Fig. 9.1 Four-field radiation technique delivering high-dose radiation to the entire pelvis including bladder and rectum

beam is modulated in such a manner that the normal structures (also labelled as organs at risk) like bowel, bladder, and rectum can be protected from high dose to reduce toxicity. Preliminary experience with IMRT has been promising, with low rates of both acute and chronic toxicity [14]. However, its use is limited to centers specialized in IMRT and it also has certain ambiguities. Especially since there is a major impact of movement of the vaginal vault due to variable bladder and rectal distension, these techniques should be adopted with caution especially under image guidance (Image Guided Radiation Therapy-IGRT). In IGRT, a real-time daily cone beam CT scan is acquired just prior to radiation delivery to verify the patients' position as well as the adequate and acceptable bladder and rectal distension. This ensures precise radiation delivery to the desired area and prevents inadvertent radiation to surrounding areas (Fig. 9.2a, b).

Dose schedule—The dose is usually 45–50.4 Gy given in 1.8–2.0 Gy fractions over 5–6 weeks. Higher dose schedule is preferred in node-positive disease, whereas in node-negative disease 45 Gy is preferred to reduce toxicity. The vaginal cuff can be boosted with vaginal brachytherapy if indicated, especially in margin positive disease, cervical involvement, and higher-grade disease. Treatment generally is initiated 4–6 weeks after surgery to allow for adequate wound healing [13].

9.2.2 Vaginal Brachytherapy

The purpose of the brachytherapy is to deliver radiation to the remnant vaginal cuff mucosa to prevent local recurrence. In this technique, the lymphatics are not treated. An applicator in the form of either vaginal ovoids or a vaginal cylinder is introduced in the vagina in such a manner that it abuts the vaginal vault. The choice of applicator for treatment of the vagina is both institutional and patient dependent. Ovoids

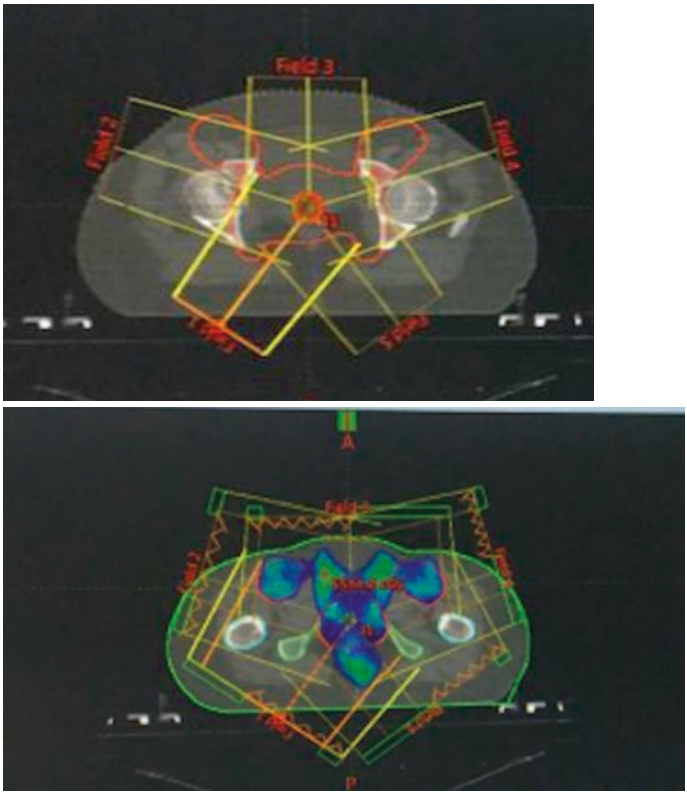


Fig. 9.2 (**a** and **b**) Intensity-modulated radiation therapy with multiple modulated fields to a CT scan localized target

treat only the upper part of the vaginal (termed the vaginal cuff), whereas vaginal cylinder allows treatment of the entire length of the vagina [15].

Additionally, a urinary catheter and a rectal tube are placed with some radiopaque material or contrast. A radiograph is acquired and the dose points are determined, these are usually placed over the vaginal mucosa or at a depth of 5 mm. Nowadays, brachytherapy is also image guided wherein instead of X-ray the planning is done after acquiring a CT scan. This helps in localizing bladder, rectum, and bowel in 3 dimensions rather than just dose points as seen in X-ray-based planning. In general, the upper two-thirds of the vagina is treated but in adverse histology like serous and clear cell carcinoma, the entire vaginal length is treated.

The radiation therapy machines can deliver radiation either by high dose rate (HDR) or low dose rate (LDR) depending upon the availability of the machine. The effective doses delivered by both dose rates are similar but there is an increasing trend toward adoption of high dose rate. This is due to the faster dose delivery which reduces the treatment time allowing it to be delivered on an out-patient basis. But it

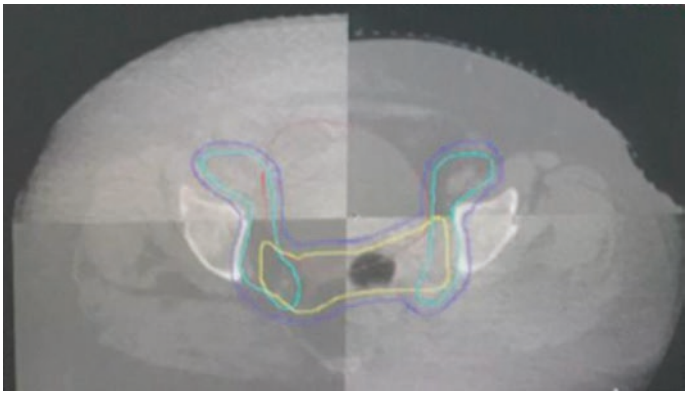


Fig. 9.3 Image-guided radiation therapy—on board imaging done to check bladder and rectal filling during radiation for better precision

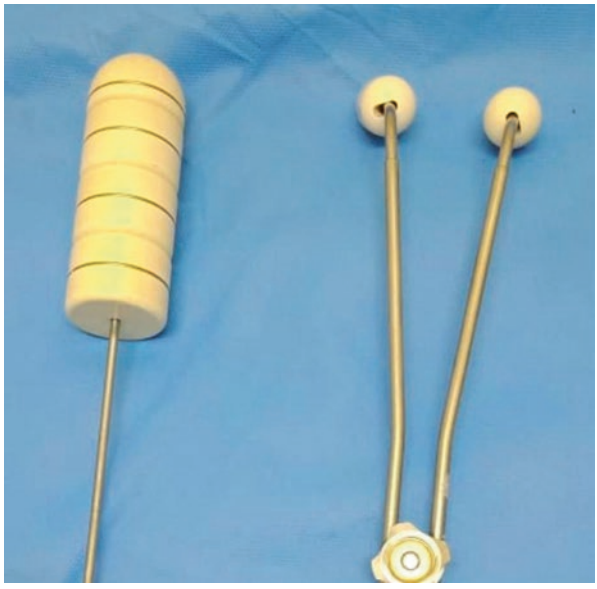


Fig. 9.4 Vaginal brachytherapy applicators (left—vaginal cylinder, right—ovoids)

adds to the number of fractions as with HDR entire dose cannot be delivered in one session (Figs. 9.3 and 9.4).

Dose Schedule—The prescription dose depends upon the number of fractions and dose specification points (to the vaginal mucosa or to a depth of 5 mm). The dose schedules advocated by the American Brachytherapy Society (ABS) or ESTRO are followed by many centers [15]. The first session of brachytherapy is timed 4–6 weeks post surgery to allow vaginal cuff healing. Some institutes prefer to wait up to 9 weeks to reduce the risk of vaginal cuff dehiscence. Vaginal brachytherapy (VBT) usually consists of three to five fractions given once or twice weekly on an

outpatient basis. Brachytherapy dose has been shown to impact vaginal toxicity. A significant reduction in vaginal length was noted in a higher dose per fraction without impacting vaginal recurrence. Seven Gy × 3 prescribed to 5-mm depth is a commonly used fractionation scheme that delivers a comparable dose for late effects to the vaginal surface when compared to the higher dose regimen [16]. This regimen may be expected to lead to increased vaginal fibrosis as compared with a lower dose per fraction regimens. Effective lower dose regimens (6 Gy × 5 or 4 Gy × 6 prescribed to the vaginal surface) have been reported with excellent vaginal control rates and minimal vaginal toxicity [15]. The fractionation schedule hence varies among practioners.

9.3 Adjuvant Radiation Therapy

The adjuvant therapy is dictated by the risk stratification as described earlier. Generally, low- and intermediate-risk disease are managed by observation and vaginal brachytherapy and high-risk disease require pelvic radiation and/or chemotherapy. Clinical guidelines have been issued by ESMO-ESTRO and ASTRO-ASCO [1, 2]. An overview of adjuvant treatment is shown in Table 9.2.

9.3.1 Low-Risk Endometrial Carcinoma

For women with low-risk endometrial cancer, no adjuvant treatment is indicated following surgery. Although radiation therapy (RT) can reduce the risk of local recurrence, it does not translate into improved overall survival. Rather it may increase the risk of treatment-related complications especially external beam radiation therapy. Although vaginal brachytherapy has lesser toxicity but it has no clear benefits.

RT was associated with an increased risk of death related to endometrial cancer when compared with observation alone (relative risk 2.64, 95% CI 1.05–6.66) in a meta-analysis of eight trials conducted in 2012 that evaluated RT for stage I

Table 9.2 Overview of adjuvant treatment

Risk group	Adjuvant therapy
Low-risk endometrial cancer	No adjuvant treatment is indicated following surgery
Intermediate-risk endometrial cancer	Low intermediate risk can be offered observation or vaginal brachytherapy High intermediate-risk endometrial cancer benefit most from postoperative radiation therapy (RT)
High-risk endometrial cancer	Should be offered adjuvant radiation therapy and/or chemotherapy Though benefit by adding chemotherapy to RT is not entirely clear, especially after the PORTEC 3 trial results Although chemotherapy is essential for the poor histology like serous carcinoma and clear cell carcinoma

endometrial cancer low-risk (n = 517) [17]. There is a lack of benefit but increased risks associated with EBRT for long-term survivors established in another study [18]. In a study conducted between 1968 and 1974, with 560 women, all patients with uterine-confined endometrial cancer underwent brachytherapy. They were further randomly assigned to pelvic EBRT versus no further treatment. At a median follow-up of 20.5 years, the study demonstrated no survival benefit with pelvic EBRT compared with women who were only under observation (hazard ratio [HR] for mortality 1.13, 95% CI 0.96–1.35). Rather it reported a higher mortality risk (HR 1.36, 95% CI 1.06–1.76) in women under 60 years who received EBRT. They also noted a higher rate of grade 2 adverse events (27 versus 5%) and grade 3 or 4 adverse events (3 versus 0%). Also, a higher risk of secondary malignancies was found in women younger than 60 years.

In another study in 645 women with stage IA EC (grade 1 to 2) who underwent surgical treatment alone or had surgery plus VBT (three to six fractions were administered over 4–15 days); total dose administered was 18.0–24.0 Gy (3–8 Gy per fraction) [19]. This multi-institutional European study failed to appreciate any difference in cancer-specific or overall survival. Rather VBT was associated with an increase in genitourinary symptoms. Since there were more risks than benefits associated with RT for patients with low-risk endometrial cancer, so no adjuvant radiation therapy is currently recommended. The incomplete nodal staging in this subgroup also does not warrant adjuvant RT as it also does not have a survival benefit.

9.3.2 Intermediate Risk

The adjuvant treatment options for women with intermediate-risk disease include observation or RT. The selection of treatment depends on further stratification based on risk factors.

In low intermediate group observation after surgery is preferred over RT. As they have a good prognosis, adjuvant RT does not give survival benefits, rather it increases the side effects significantly. This was studied in GOG 99 trial, which randomized 448 women with intermediate-risk endometrial cancer to adjuvant pelvic RT or observation [5]. Adjuvant pelvic RT reduced the incidence of first recurrence compared with observation only (hazard ratio [HR] 0.46, **90%** CI 0.19–1.11), which was not statistically significant. But it could not appreciate the difference in the incidence of distant recurrence and the risk of death due to endometrial cancer. The overall incidence of death was low (3 versus 2%, respectively) but a significantly higher number of moderate to serious (grade 2–4) toxicity, including hematologic (14 versus 5%), gastrointestinal (64 versus 5%), and cutaneous toxicity (15 versus 9%) were observed. Gastrointestinal toxicity included serious gastrointestinal obstruction in six patients treated with RT compared with one patient in the observation arm.

In high intermediate-risk disease, radiation therapy is preferred over observation due to risk of a local recurrence. This risk is significantly reduced with adjuvant RT

although it may not translate into OS advantage. In a meta-analysis conducted in 2012, assessing the role of adjuvant RT among women with stage I endometrial cancer, there was no significant difference in OS (HR 0.88, 95% CI 0.63–1.22) or cancer-specific survival (HR 0.80, 95% CI 0.54–1.18) [17]. Whereas GOG 99 demonstrated the benefit of adjuvant RT for lowering the risk of a local recurrence [5]. Pelvic RT resulted in a reduction in the risk of a local recurrence compared with observation (2 versus 9%, HR 0.42, 90% CI 0.21–0.83). Despite this, there was no statistically significant reduction in the risk of death (HR 0.73, 90% CI 0.43–1.26), although the study was not powered sufficiently for this endpoint. Because of the apparent lack of a significant OS advantage with adjuvant RT, some experts prefer not to administer adjuvant RT in this population.

Radiation therapy can be administered as VBT or pelvic external beam RT. Despite the fact that pelvic RT decreases the risk of a local recurrence, it is associated with more long-term GI and genitourinary toxicity. Most technically advanced centers deliver external radiation therapy by IMRT due to its ability to reduce high doses to small bowel, bone marrow, bladder, and rectum. This reduces the incidence of grade 2 and 3 gastrointestinal and hematological toxicity, although there is no randomized trial to establish this superiority over the conformal radiation techniques. The degree to which IMRT can reduce these symptoms is the focus of an ongoing randomized RTOG study, TIME-C, which is comparing IMRT to standard pelvic radiation.

IMRT despite being an attractive alternative is not widely available. Vaginal brachytherapy is a better modality for high intermediate-risk endometrial cancer patients. It yields comparable locoregional recurrence rates compared with pelvic RT and at the same time has a favorable toxicity profile [20]. This has been substantiated by the Post-Operative Radiation Therapy in Endometrial Cancer (PORTEC)-2 trial results. In this trial, 427 women with high intermediate-risk disease were randomized to adjuvant VBT or pelvic RT [21]. There was no statistically significant differences in locoregional recurrence (5 versus 3% for VBT and pelvic RT, respectively), distant metastasis (8 versus 6%, or 5 year) disease-free survival (83 versus 78%, respectively) and OS (85 versus 80%, respectively) at 45 months. VBT was associated with a significantly lower rate of GI toxicity (13 versus 54%, respectively). More bowel and bladder symptoms impacting the daily activities were noted in longer-term follow-up (7 years), patients receiving pelvic RT. Although it did not lead to a decline in quality of life scores.

Incomplete nodal staging in this subgroup requires nodal irradiation if reoperation to complete formal staging is not contemplated. RT can be safely delivered instead of surgery and this is supported by the PORTEC data [22–26]. 715 women who did not have complete nodal dissection were randomized to adjuvant pelvic RT or observation There was no significant difference in 15-year OS in both groups although a significantly lower locoregional recurrence rate (5 versus 16%) was observed. Also, there was a nonsignificant difference in the rate of distant metastases as well as in the rate of second primary cancers at 15 years.

9.3.3 High-Risk Group

This is a heterogeneous group and includes high-risk histology (serous adenocarcinoma and clear cell adenocarcinoma irrespective of stage), grade 3 deeply invasive endometrioid carcinoma and pathologic stages III/IV disease (irrespective of histology). Due to heterogeneity of the disease and lack of robust data to formulate recommendations, there is no uniform approach. Most trials have too few patients with clear cell endometrial cancer for definitive conclusions about the treatment of this histologic subtype [1, 2].

9.3.4 Noninvasive Stage IA Disease

Women with stage IA disease without myometrial invasion (clear cell or serous histology) may be kept only on observation. However, alternatively, adjuvant vaginal brachytherapy may be offered, depending on institutional practices. The rationale for vaginal brachytherapy in noninvasive serous tumors is that there can be up to a 10% risk of vaginal cuff recurrences.

A review of cases of stage IA polyp- or endometrium-limited endometrial cancers of clear cell, serous, or mixed histology who received a variety of adjuvant therapies like chemotherapy with or without RT (intravaginal or pelvic), RT (intravaginal or pelvic) alone, or no adjuvant treatment showed a 3-year progression-free survival (PFS) rate of 94.9%. Adjuvant therapy did not impact overall survival (OS) or PFS [27].

9.3.5 Invasive Stage IA, IB, or II Disease

Women with stage IA disease with myometrial invasion, stage IB or II serous carcinoma, or high-grade IB endometrioid carcinoma may be offered pelvic radiation therapy (RT) alone or vaginal brachytherapy with adjuvant chemotherapy.

Given similar efficacy but improved tolerability with pelvic RT, some institutes prefer pelvic RT. GOG-249 conducted a phase III trial which observed that recurrence-free and overall survival rates for stage I and II high-risk endometrial cancer were not superior after adjuvant brachytherapy and chemotherapy when compared with adjuvant pelvic radiation therapy [28]. In this trial, 601 women with high intermediate-risk or high-risk, early-stage (I and II) endometrial cancer were randomized to vaginal brachytherapy followed by three cycles of paclitaxel/carboplatin chemotherapy or to pelvic RT alone [29]. The two arms had comparable 36-month recurrence-free survival (both 82%) and 36-month OS (88 versus 91%). Risk of pelvic and para-aortic nodal recurrence and frequency of short-term side effects was higher in brachytherapy–chemotherapy arm. The late toxicity was comparable across groups (12 and 13%).

There is an ongoing ENGOT-EN2-DGCG trial, which randomly assigns women with stage I clear cell, serous, or grade 3 tumors with surgically negative nodes to

chemotherapy with six cycles of carboplatin/paclitaxel or no prescribed adjuvant therapy [30]. Use of vaginal brachytherapy is optional in either arm; no pelvic RT is used.

9.3.6 Stage III Disease

For most women with stage III or resectable stage IV endometrial cancer, some authors suggest adjuvant chemotherapy, with or without vaginal brachytherapy, rather than whole-pelvic RT. Chemotherapy is usually done for six cycles. For women who undergo adjuvant chemotherapy, especially those with deep invasion or bulky lymphadenopathy, sometimes vaginal brachytherapy is performed to control local recurrence. For patients who are not candidates for chemotherapy, whole-pelvic RT is preferred. Additionally, data are limited for those with clear cell carcinoma, and while most institutions do not alter their usual approach, others offer radiation with or without chemotherapy for this histology.

The PORTEC-3 trial enrolled women with high-risk stage I disease (grade 3 with deep myometrial invasion and/or lymphovascular invasion), stage II or III disease, or tumors with serous or clear cell histology; stage III comprised almost half of the cases [31, 32]. Patients were randomized to receive chemoradiation (CTRT) (two cycles of 3 weekly cisplatin with pelvic RT, followed by four cycles of carboplatin and paclitaxel) or to pelvic RT alone. There was an improved 5-year failure-free survival in the CTRT group, which was specifically seen among those with women with a high risk of local relapse (e.g., those with extensive lymph node involvement or deep invasion) stage III disease (HR 0.66, 95% CI 0.45–0.97). Although there was no statistically significant difference in OS in any subset at a median follow-up of approximately 60 months and did not improve survival when compared with chemotherapy in the GOG-258 trial. Grade 3 or higher adverse events, especially hematologic (45%) were more frequent with CTRT versus RT alone (61 versus 13%).

GOG-258 studied 700 patients with stage III to IVA (with <2 cm residual) disease or stage I/II serous or clear cell endometrial carcinoma (FIGO 2009) [33]. Patients were randomized to receive either chemotherapy alone (6 cycles of carboplatin and paclitaxel) or CTRT (External radiation with concurrent cisplatin followed by 4 cycles of carboplatin and paclitaxel). No advantage in relapse-free survival or OS was observed at a median follow-up of 47 months. Although there were fewer lower vaginal recurrences with the addition of radiation (3 versus 7%; HR 0.36, 95% CI 0.16–0.82), and fewer lower pelvic and para-aortic relapses (10 versus 19%; relative risk 0.43, 95% CI 0.28–0.66). Distant recurrence rate was higher in the CTRT arm (28 versus 21%; HR 1.36, 95% CI 1.0–1.86). Rates of ≥grade 3 toxicities were similar between the arms, while quality of life was slightly inferior in the CTRT arm.

Based on the PORTEC 3 data for the case where adjuvant radiation therapy is planned, it is important to do a proper sequence of RT and chemotherapy. Acceptable approaches include giving RT after completion of six cycles of chemotherapy,

"sandwiched" in-between three cycles of chemotherapy before and after RT, or concurrently, as in GOG-258 and PORTEC-3. Sequential or concurrent approach is preferable as there is no robust data supporting the sandwich technique.

9.3.7 Stage IV Disease

Women with unresectable stage III or IV disease are treated with chemotherapy. The role of pelvic RT in these women must be individualized based on the burden of disease. At times role of radiation therapy is limited to palliative therapy only.

In patients with limited disease in the pelvis, surgical cytoreduction may be performed. This is usually followed by adjuvant chemotherapy. Although there is no randomized data in this context but retrospective data shows better outcomes in patients who underwent with optimal debulking [34–36].

9.4 Summary

Adjuvant radiation therapy in surgically staged carcinoma endometrium is risk adaption based. The treatment is now better defined in low and intermediate-risk groups where the data has been conclusive. There is a trend towards de-intensification of therapy as these subgroups have a good prognosis. The role of adjuvant therapy is still not clearly defined for high-risk patients as this is a heterogeneous group. Additionally, the observations from various trials are unable to replicate results, some trials have established improvement in local control and survival with concurrent chemoradiation in many subgroups whereas others failed to find any advantage of addition of chemotherapy to radiation. The most awaited PORTEC 3 also could not clear grounds for either of therapy. So, till date adjuvant therapy in the high risk is risk-adapted weighing the benefit against the toxicities. Although with the new image-guided techniques there is a reduction in the toxicities and the newer trials should include the contemporary radiation techniques to explore the real benefit in this subgroup of patients. The newer molecular markers may draw light on the better risk prognostication and decision-making in this subgroup.

References

1. 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.
2. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, Marth C, Nout R, Querleu D, Mirza MR, Sessa C. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Ann Oncol. 2016;27:16–41.
3. Abu-Rustum NR, Zhou Q, Gomez JD, et al. A nomogram for predicting overall survival of women with endometrial cancer following primary therapy: toward improving individualized cancer care. Gynecol Oncol. 2010;116:399.

4. Alektiar KM, Venkatraman E, Abu-Rustum N, Barakat RR. Is endometrial carcinoma intrinsically more aggressive in elderly patients? Cancer. 2003;98:2368.
5. Keys HM, Roberts JA, Brunetto VL, 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;92:744.
6. Lee NK, Cheung MK, Shin JY, et al. Prognostic factors for uterine cancer in reproductive-aged women. Obstet Gynecol. 2007;109:655.
7. Mundt AJ, Waggoner S, Yamada D, et al. Age as a prognostic factor for recurrence in patients with endometrial carcinoma. Gynecol Oncol. 2000;79:79.
8. 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;99:564.
9. Wethington SL, Barrena Medel NI, Wright JD, Herzog TJ. Prognostic significance and treatment implications of positive peritoneal cytology in endometrial adenocarcinoma: unravelling a mystery. Gynecol Oncol. 2009;115:18.
10. Garg G, Gao F, Wright JD, et al. Positive peritoneal cytology is an independent risk-factor in early stage endometrial cancer. Gynecol Oncol. 2013;128:77.
11. Myers AP. New strategies in endometrial cancer: targeting the PI3K/mTOR pathway--the devil is in the details. Clin Cancer Res. 2013;19:5264.
12. Mackay HJ, Eisenhauer EA, Kamel-Reid S, et al. Molecular determinants of outcome with mammalian target of rapamycin inhibition in endometrial cancer. Cancer. 2014;120:603.
13. Sharma K, Rathi AK. Step by step radiation therapy: treatment and planning: Jaypee Brothers Medical Publishers; 2016.
14. Beriwal S, Jain SK, Heron DE, et al. Clinical outcome with adjuvant treatment of endometrial carcinoma using intensity-modulated radiation therapy. Gynecol Oncol. 2006;102:195.
15. Small W Jr, Beriwal S, Demanes DJ, Dusenbery KE. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. Brachytherapy. 2012;11:58–67.
16. Sorbe BG, Smeds AC. Postoperative vaginal irradiation with high dose rate after loading technique in endometrial carcinoma stage I. Int J Radiat Oncol Biol Phys. 1990;18:305–31.
17. Kong A, Johnson N, Kitchener HC, Lawrie TA. Adjuvant radiotherapy for stage I endometrial cancer. Cochrane Database Syst Rev. 2012:CD003916.
18. Onsrud M, Cvancarova M, Hellebust TP, et al. Long-term outcomes after pelvic radiation for early-stage endometrial cancer. J Clin Oncol. 2013;31:3951.
19. Sorbe B, Nordström B, Mäenpää J, et al. Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: a controlled randomized study. Int J Gynecol Cancer. 2009;19:873.
20. Alektiar KM, Venkatraman E, Chi DS, Barakat RR. Intravaginal brachytherapy alone for intermediate-risk endometrial cancer. Int J Radiat Oncol Biol Phys. 2005;62:111.
21. Nout RA, Smit VT, Putter H, 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;375:816.
22. 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;355:1404.
23. Creutzberg CL, van Putten WL, Koper PC, 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;51:1246.
24. Creutzberg CL, Nout RA, Lybeert ML, et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. Int J Radiat Oncol Biol Phys. 2011;81:e631.
25. Parthasarathy A, Kapp DS, Cheung MK, et al. Adjuvant radiotherapy in incompletely staged IC and II endometrioid uterine cancer. Obstet Gynecol. 2007;110:1237.
26. Scholten AN, van Putten WL, Beerman H, et al. Postoperative radiotherapy for stage 1 endometrial carcinoma: long-term outcome of the randomized PORTEC trial with central pathology review. Int J Radiat Oncol Biol Phys. 2005;63:834.

27. 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;26:497.
28. McMeekin DS, Filiaci VL, Aghajanian C, et al. Randomized phase III trial of pelvic radiation therapy (PXRT) versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy (VCB/C) in patients with high risk (HR), early stage endometrial cancer (EC): a gynecologic oncology group trial. Gynec Oncol. 2014;134:438.
29. Randall M, Filiaci V, McMeekin D, et al. A phase III trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin chemotherapy in patients with high-risk, early stage endometrial cancer: a gynecology oncology group study. Int J Radiat Oncol Biol Phys. 2019;37(21):1810–8.
30. Bernardini MQ, Gien LT, Lau S, et al. Treatment related outcomes in high-risk endometrial carcinoma: Canadian high risk endometrial cancer consortium (CHREC). Gynecol Oncol. 2016;141:148.
31. de Boer SM, Powell ME, Mileshkin L, et al. Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2018;19:295.
32. de Boer SM, Powell ME, Mileshkin L, et al. Toxicity and quality of life after adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol. 2016;17:1114.
33. Matei D, Filiaci VL, Randall M, Steinhoff M. A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma. J Clin Oncol. 2017;35S:5505.
34. Patsavas K, Woessner J, Gielda B, et al. Optimal surgical debulking in uterine papillary serous carcinoma affects survival. Gynecol Oncol. 2011;121:581.
35. Rauh-Hain JA, Growdon WB, Schorge JO, et al. Prognostic determinants in patients with stage IIIC and IV uterine papillary serous carcinoma. Gynecol Oncol. 2010;119:299.
36. Shih KK, Yun E, Gardner GJ, et al. Surgical cytoreduction in stage IV endometrioid endometrial carcinoma. Gynecol Oncol. 2011;122:608.

Part III

Newer Advances

Fertility Preserving Options in Endometrial Cancer

10

Bindiya Gupta

10.1 Introduction

Endometrial cancer is one of the commonest gynecologic malignancies in the Western world and according to the World Cancer Research Fund, endometrial cancer is the sixth most common cancer in women with approximately 380,000 new cases in 2018 [1]. According to GLOBOCAN 2018, worldwide, the incidence and mortality ASR was 8.4 per 100,000 women and 1.8 per 100,000 females, respectively [2]. Although it is predominantly seen in postmenopausal women, it is increasingly diagnosed in women <40 years. 14% of cases still occur in premenopausal women, with 5% occurring in women under 40 years of age [3]. According to the SEER statistics report, around 7.6% of cases occurred between 20 and 44 years of age [4].

However, younger patients have excellent prognosis as they usually have type 1 endometrial cancer. These are usually well differentiated, low grade endometrioid adenocarcinoma that is estrogen dependent, and have an indolent course. These are generally associated with precursor lesions like atypia and hyperplasia and have estrogen, progesterone, and androgen receptor positivity [5].

10.2 Risk Factors

(a) *Obesity*: It is one of the most important risk factors in young women. A high BMI >35 has a 2–4 fold increase risk of endometrial cancer [4]. The risk reduces by 20% in women who engage in an active lifestyle [6]. Obesity increases estrogen levels by peripheral conversion in adipose tissues and also increases predisposition to Type 2 diabetes and hyperinsulinemia. The latter promotes proliferation of tumor cells.

B. Gupta (✉)
Obstetrics and Gynecology, UCMS & GTB Hospital, Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_10

(b) *Genetic*: Approximately 5% of EC cases are caused by genetic mutations and typically occur 10–20 years before sporadic EC. Lynch syndrome (LS; hereditary nonpolyposis colorectal cancer) is an autosomal dominant syndrome with a lifetime risk of 60% of developing endometrial cancer [7]. It results from a germline mutation in one of four DNA mismatch repair genes (MLH1, MSH2, MSH6, or PMS2). In LS, EC occurs significantly more commonly in patients with early menarche, nulliparity, short-term, or no oral contraception (1 year) [8].

American Cancer Society and National Comprehensive Cancer Network (NCCN) recommends annual EC screening with endometrial biopsy starting at age 35 years. Transvaginal sonography is not recommended as a screening tool due to normal variations of endometrial thickness in menstruating women, which could lead to unnecessary imaging and procedures [9].

(c) *Others*: Other risk factors of endometrial cancer in younger women <45 years include nulliparity, chronic anovulation like polycystic ovarian syndrome, early menarche, and hypertension [10]. These women also have a history of infertility.

10.3 Selection Criteria for Conservative Management

Women undergoing conservative management should be preferably under 40 years of age with a desire to plan and achieve pregnancy soon after tumor regression.

The eligibility criteria for women offered conservative management is as follows [11]:

1. Grade 1 well-differentiated adenocarcinoma on D&C specimen.
2. Absence of lymphovascular space invasion on curettage specimen.
3. No myometrial invasion, no extension to the cervix, on magnetic resonance imaging (MRI) preferably, or on transvaginal sonography.
4. No suspicious metastatic disease including pelvic and para-aortic lymphadenopathy on workup.
5. No adnexal mass on imaging.
6. Preferably the presence of strong and diffuse expression of progesterone receptor on immunohistochemistry. However, this is not routinely done as studies have shown that receptor-negative women also show an effective response to therapy [12]. PTEN gene and phospho-AKT expression are associated with a good response to progestogen therapy. MLH1 gene in tissues with complex endometrial hyperplasia is associated with high risk of failure and progression to endometrial cancer.

There should be no contraindication to high dose oral progestogens and patient should be able to tolerate high doses. Although there is no document to address the absolute contraindications, the guide for progestin-only oral contraceptives can be used a reference. Category 3 or 4 contraindications include history of current breast cancer, liver disease (i.e., severe cirrhosis) or liver tumors (hepatocellular adenoma

or hepatoma) or use of medications (i.e., phenytoin, carbamazepine, barbiturates, primidone, topiramate, oxcarbazepine, or rifampicin).

10.4 Counselling

Counselling sessions should be teamwork of gynecologists, oncologists, infertility specialists, and psychosocial experts and should involve the woman's family with a carefully written down plan, before initiation of treatment. The economic burden and feasibility should be included in the decision-making process.

Women should be counselled that medical treatment is not the definitive treatment modality and lacks good scientific evidence. The woman should be encouraged to opt for assisted reproductive techniques soon after remission to achieve pregnancy as soon as possible and at the same time should be willing for completion surgery once childbearing is complete. Extensive counselling about conservative management includes the success and relapse rates, risk of metastasis, and side effects of hormones. The patient should be advised to be compliant with follow-up protocols, need for repeated sampling of the endometrium and consequent risk of Asherman's syndrome. Patients with Lynch syndrome or HNPCC or autosomal dominant cancer syndromes (like Cowden syndrome) should be referred for genetic counselling so that the woman and her relatives can be given education and information on prevention strategies and any intervention instituted.

10.5 Pre-treatment Evaluation

1. *Endometrial sampling*: Studies have confirmed that dilatation and curettage is the procedure of choice for evaluating tumor grade. Data has shown that after dilatation and curettage or fractional curettage only 10% of samples are upgraded following hysterectomy compared to 26% after office sampling [13]. Endometrial biopsy using Vabra aspirator, Pipelle, and Karman cannula has a variable sensitivity of 68–92% and a false positive rate of 10% [14]. Addition of hysteroscopy to sampling has the advantage of visually guided biopsies and identification and removal of focal lesions with a sensitivity and specificity of 80–98% and 92–96%, respectively [15, 16].
2. *Imaging:* Transvaginal ultrasound (TVS) helps in evaluation of endometrial thickness, uterine lesions, myometrial invasion, and adnexal involvement but is limited by its inability to evaluate the pelvic and para-aortic nodes. Contrast-enhanced MRI has a high diagnostic accuracy for detection of myometrial invasion and cervical extension, with 95% sensitivity, 60–70% specificity and a total accuracy of 88–90% [17, 18]. In contrast, the accuracy, sensitivity, and specificity of TVS in a study was 69%, 61%, and 89% [19]. MRI or contrast-enhanced MRI is the preferred modalities for evaluation of the presence of myometrial invasion. The sensitivity and specificity of detection of lymph node involvement

are 72% and 92%, respectively [20]. Positron emission tomography has a limited role in conservative management.

3. *Others:* Up to 10% of synchronous ovarian tumors may be present in endometrial cancer. As ovarian malignancy can be missed in up to 9–14% cases even on MRI, a diagnostic laparoscopy can be considered in suspected cases. The latter also has the advantage of lymph node biopsy when suspected on imaging.

10.6 Treatment Modalities

10.6.1 Progestogens

Currently, progestogens administered for endometrial carcinoma include oral preparations like medroxyprogesterone acetate (MPA) and megestrol acetate (MA) or levonorgestrel delivered by levonorgestrel intrauterine system (LNG IUS).

10.6.1.1 Mechanism of Action

Out of the two progesterone receptors namely α and β, the latter is more abundant and more important in the management of endometrial cancer. Effect of progesterone on α receptor induces cell senescence, while its effect on the β receptor induces secretory differentiation and inhibits in vitro human endometrial cancer cell growth. Both isoforms promote apoptosis and induce cell cycle inhibition [21]. Continuous use of exogenous progestogens also downregulates both estrogen receptors and progesterone receptors. Progestogens also enhance p27 expression resulting in inhibition of cyclin–E–Cdk2 function and suppression of cell cycle.

10.6.1.2 Oral Progestogens

The recommended dose of medroxyprogesterone acetate is 400–600 mg per day and megestrol acetate is 160 mg/day or 80 mg twice a day. Usually, response is seen within 12 weeks of starting oral progesterone therapy, but it may even take up to 9 months [22]. It is recommended to use progestins continuously for 3 months and a repeat hysteroscopy guided sampling is recommended at 3 months [23].

Side effects include liver dysfunction and venous thromboembolism. Less serious side effects of high-dose progestins include headaches, breast tenderness, nausea, dizziness, weight gain, acne, thrombosis, and hair growth on the face and body [24].

10.6.1.3 Levonorgestrel Intrauterine System

In contrast to oral therapy, Levonorgestrel Intrauterine System (LNG IUS) has several benefits. As the serum level of progestin is lower with LNG IUS, the risk of most side effects as weight gain and thrombosis is much lower. As this device involves single time insertion it ensures better compliance [25].

Experience with the use of LNG IUS alone in the setting of endometrial cancer is still limited, and largely based on observational studies and retrospective evidence. In a Cochrane review in 2018, they concluded that evidence till date is from

a subgroup of 19 women in a larger RCT. Regression was 100% in all six women who used the LNG IUS system but there was insufficient evidence to draw any conclusions regarding the relative efficacy of LNG IUS versus oral progesterone (MPA) in this group of women [26].

A recent meta-analysis comparing LNG IUS with oral progesterone for non-atypical endometrial hyperplasia has shown that LNG IUS is associated with greater regression of histology, lower relapse rates, and lower rates of hysterectomy [27]. The odds ratio [OR] of comparative therapeutic response rates after 3, 6, 12, and 24 months of treatment were [OR], 2.30; 95% confidence interval [CI], 1.39–3.82; $P = 0.001$, OR, 3.16; 95% CI, 1.84–5.45; $P < 0.00001$, OR, 5.73; 95% CI, 2.67–12.33; $P < 0.00001$ and OR, 7.46; 95% CI, 2.55–21.78; $P = 0.0002$, respectively. Quality of life data meta-analysis also confirms that the incidence of weight gain, mood disturbances, headaches, and sleep disorders is less with LNG IUS compared to oral progestogens.

A recent retrospective study on LNG IUS showed response rates of 80% (95% confidence interval [CI] = 52–96) in atypical hyperplasia patients ($n = 15$), 67% (95% CI = 30–93) in early endometrial cancer grade 1 ($n = 9$) and 75% (95% CI = 35–97) in grade 2 patients ($n = 8$) [28].

Till date in the largest retrospective series, LNG IUS alone achieved a complete response rate of 89.3% in atypical hyperplasia, 81.3% in endometrial cancer grade 1 patients, and 75% in grade 2 patients [29]. There are two ongoing clinical trials in MD Anderson for the efficacy of LNG IUS.

Studies have also reported success of 50% with a combination of LNG IUS and gonadotropin-releasing hormone analogue [30]. Aromatase inhibitors have also been used in combination with progestogens in research studies.

10.6.2 Hysteroscopic Resection Combined with Progestogen Therapy

A three-step hysteroscopic resection has been described by Mazzon et al. with a pathological analysis at each step. First step consisted of removal of the tumor, second step is the removal of the adjacent endometrium, and final step is the removal of the myometrium underlying the tumor [31]. This was followed by administration of 160 mg of Megestrol acetate. However, it is associated with theoretical risk of tumor dissemination, risk of intrauterine adhesions, and pregnancy complications like morbid adherent placenta related to resection and there is insufficient evidence to recommend it in routine practice.

In a small study of nine women, which combined hysteroscopic resection with LNG IUS, there were no complications and all women had a 100% regression rate after 6 months. At 5-years follow-up there was no sign of recurrence [32].

A recent review of the literature reported a recurrence rate of 11% after a median follow-up period of 40 months (range: 11–82 months) after hysteroscopic resections of endometrial lesions and subsequent hormonal therapy with oral and/or IUD progestins [33].

10.7 Monitoring After Conservative Management

There is no well-defined protocol of follow-up after conservative management, and it varies in different institutions. As the time of response to therapy is variable (4 weeks–60 weeks), with a median duration of 12 weeks, a repeat imaging (Transvaginal sonography), hysteroscopy and biopsy should be performed after 6 months. Endometrial thickness of less than 5 mm is suggestive of response. Consultation with specialists in reproductive medicine should be taken to achieve pregnancy soon after remission [34–36].

If no cancer is detected at this point of time, treatment should be continued for three more months to consolidate the response. Maintenance treatment should be given to responders who wish to delay pregnancy. Additionally, complications of hormone therapy like deep vein thrombosis should be ruled out.

In case of tumor progression or persistence of disease, the patient should be counselled regarding hysterectomy, a repeat MRI can be done to revise staging, and standard surgical management is performed. Patients not undergoing hysterectomy should be evaluated clinically every 6 months [37]. After completion of childbearing, a completion surgery is recommended. Preservation of ovaries can depend on age and genetic factors.

10.8 Response to Therapy

In a systematic meta-analysis, Gunderson et al. (2012) analyzed 45 studies and showed that overall 77% women showed response to hormone therapy with a 39-month complete response rate of 53% with a median time of response of 6 months (range 1–18 months). For endometrial cancer persistent disease was observed in 25.4% while recurrence was seen in 35.4%. The complete response rate was significantly higher for those with hyperplasia than for women with carcinoma (65.8% vs. 48.2%, $p = 0.002$) [37].

In another recent meta-analysis of 34 observational studies, Gallos et al. reported that fertility sparing hormonal treatment was associated with a pooled regression rate of 76.2%, relapse rate of 40.6% and live birth rate of 28% [38]. Second cycle of progestogen therapy is associated with a response rate of 89% [39].

In a systematic review of 26 studies by Pierrati M et al. after a median follow-up of 39 months, the complete regression rate was 76.5%, with a relapse rate of 33.5% between patients who had a complete response (CR). 21.7% did not respond to therapy. Of these patients, 50.8% showed stable disease and 49% showed progressive disease while 2% experienced partial remission [40].

Presence of occult extrauterine or ovarian metastasis, lymph node involvement, and presence of synchronous ovarian tumor is the most common reasons for non—responders to treatment.

10.9 Ovarian Preservation during Hysterectomy

Ovarian preservation and hysterectomy alone gives an option of oocyte retrieval with surrogacy for childbearing and is labelled as partial preservation of fertility [10]. Moreover, it also helps delay menopause. However, it is associated with risks of missing out a synchronous ovarian malignancy or an occult metastatic disease in the ovaries. Up to 22% of young women with stage I cancers may have extrauterine disease and a 5–25% incidence of any stage synchronous ovarian malignancy, which is at least five times greater than women older than 45 years [41].

In a study of 251 women, younger than 45 years, 75.3% had FIGO stage I disease, there was no statistically significant difference in overall survival and disease-free survival in Stage I patients with or without BSO [42]. According to the data of SEER study, 5-year survival was 98% for patients with 1988 FIGO IA endometrial cancers, with or without ovarian preservation [43]. Among patients with 1988 FIGO IC (2009 FIGO IB) endometrial cancer, survival was 89% in the oophorectomy group and 86% with ovarian preservation which was not statistically significant.

10.10 Management of Infertility and Reproductive Outcomes

All efforts should be made to achieve successful conception soon after histological remission is achieved which is usually by 16 weeks of therapy and assisted reproductive techniques (ART) must be offered [36]. Ovulation induction, Intrauterine insemination (IUI), or in vitro fertilization (IVF) is recommended. The latter has an added advantage of cryopreservation of embryos for future cycles. Failure to achieve pregnancy after ART may be due to an impaired endometrial response because of primary endometrial disease, repeated endometrial samplings, and thin endometrium due to high-dose progestin treatment [44].

In a systematic review in 2013, out of 152 patients, 60% had a successful pregnancy with a live birth rate of 70%. There was no increase in spontaneous abortions or ectopic pregnancy. Pregnancy rates were significantly higher after ART as compared to spontaneous conceptions (80.0% vs. 43.2%). In the ART group, 7.1% conceived on ovulation induction, while conceptions after IUI and IVF were 21.4% and 71.4%, respectively [45]. A recent study from Japan reported a high rate (7%) of placenta accreta in these patients and 24% relapse rate after delivery [46].

In a systematic review of 26 studies by Pieretti et al., out of 162 women who desired pregnancy, the pregnancy rate was 73.4%, which included women who conceived both spontaneously (54 pregnancies) and via ART (65). Of the 119 analyzed pregnancies, 105 live births occurred (54 from ART).

To conclude, there are oncologic risks and therapeutic challenges in conservative management of endometrial cancer in younger women. There is a strict selection criteria and extensive counselling is required. Close surveillance should be done post therapy and completion surgery is offered once family is completed.

10.11 Key Points

- Conservative management can be offered in women less than 40 years, desirous of fertility, with grade 1 adenocarcinoma confined to endometrium with no lymphovascular space invasion or cervical involvement.
- Pre-treatment evaluation includes office hysteroscopy with endometrial sampling and imaging, usually an MRI. Contrast-enhanced MRI is done for determining the size of tumor, presence of myometrial invasion, adnexal involvement, and lymph node metastasis. Alternatively, places where MRI is not avaialble, transvaginal sonography may be used.
- Progestins are the standard treatment in the form of oral progestogens namely medroxyprogesterone acetate and megestrol acetate. Intrauterine progesterone or LNG IUS with or without gonadotropins may also be used; however, evidence is limited. Hysteroscpic resection of tumor has also been done in resaerch settings.
- Hysterectomy with removal of ovaries is recommended after childbearing is complete.

References

1. Endometrial cancer statistics. https://www.wcrf.org/dietandcancer/cancer-trends/endometrial-cancer-statistics. Accessed 23 October 2019.
2. Cancer today: data visualization tool for exploring the global cancer burden in 2018. http://gco.iarc.fr/today/home. Accessed 23 October 2019.
3. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet. 2016;387:1094–108.
4. Howlader N, et al. SEER Cancer Statistics Review, 1975-2008. 2011 [cited 2011; based on November 2010 SEER data submission]. http://seer.cancer.gov/csr/1975_2008/
5. Benshushan A. Endometrial adenocarcinoma in young patients: evaluation and fertility-preserving treatment. Eur J Obstet Gynecol Reprod Biol. 2004 Dec 1;117(2):132–7.
6. Schmid D, Behrens G, Keimling M, Jochem C, Ricci C, Leitzmann M. A systematic review and meta-analysis of physical activity and endometrial cancer risk. Eur J Epidemiol. 2015;30(5):397–412.
7. Aaltonen MH, Staff S, Mecklin JP, Pylvänäinen K, Mäenpää JU. Comparison of lifestyle, hormonal and medical factors in women with sporadic and lynch syndrome-associated endometrial cancer: a retrospective case-case study. Mol Clin Oncol. 2017;6(5):758–64.
8. Dashti SG, Chau R, Ouakrim DA, Buchanan DD, Clendenning M, Young JP, et al. Female hormonal factors and the risk of endometrial cancer in lynch syndrome. JAMA. 2015;314:61–71.
9. Gupta S, Provenzale D, Regenbogen SE, et al. NCCN guidelines insights: genetic/familial high-risk assessment: colorectal. Version 3.2017. J Natl Compr Cancer Netw. 2017;15:1465–75.
10. Barry JA, Azizia MM, Hardiman PJ. Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2014;20(5):748–58.
11. Koh WJ, Abu-Rustum NR, Bean S, Bradley K, Campos SM, Cho KR, et al. Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2018;16(2):170–99.
12. Rodolakis A, Biliatis I, Morice P, Reed N, Mangler M, Kesic V, Denschlag D. European society of gynecological oncology task force for fertility preservation: clinical recommendations for fertility-sparing management in young endometrial cancer patients. Int J Gynecol Cancer. 2015;25(7):1258–65.

13. 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.
14. Leitao MM Jr, Kehoe S, Barakat RR, et al. Comparison of D&C and office endometrial biopsy accuracy in patients with FIGO grade 1 endometrial adenocarcinoma. Gynecol Oncol. 2009;113:105–8.
15. van Dongen H, de Kroon CD, Jacobi CE, Trimbos JB, Jansen FW. Diagnostic hysteroscopy in abnormal uterine bleeding: a systematic review and metaanalysis. BJOG. 2007;114(6):664–75.
16. Ceci O, Bettocchi S, Pellegrino A, Impedovo L, Di VR, Pansini N. Comparison of hysteroscopic and hysterectomy findings for assessing the diagnostic accuracy of office hysteroscopy. Fertil Steril. 2002;78(3):628–31.
17. Kaneda S, Fujii S, Fukanaga T, et al. Myometrial invasion by endometrial carcinoma: evaluation with 3.0T MR imaging. Abdom Imaging. 2011;36:612–8.
18. Vasconcelos C, Félix A, Cunha TM. Preoperative assessment of deep myometrial and cervical invasion in endometrial carcinoma: comparison of magnetic resonance imaging and histopathologic evaluation. J Obstet Gynaecol. 2007;27:65–70.
19. 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.
20. Selman TJ, Mann CH, Zamora J, et al. A systematic review of tests for lymph node status in primary endometrial cancer. BMC Womens Health. 2008;8:8.
21. Yang S, Thiel KW, Leslie KK. Progesterone: the ultimate endometrial tumor suppressor. Trends Endocrinol Metab. 2011;22:145–52.
22. Hahn H-S, Yoon S-G, Hong J-S, et al. Conservative treatment with progestin and pregnancy outcomes in endometrial cancer. Int J Gynecol Cancer. 2009;19:1068–73.
23. McKenzie ND, Kennard JA, Ahmad S. Fertility preserving options for gynecologic malignancies: a review of current understanding and future directions. Crit Rev Oncol Hematol. 2018;132:116–24.
24. Corfman PA. Labeling guidance text for progestin-only oral contraceptives. Contraception. 1995;52:71–6.
25. Chen X. The current situation of the levonorgestrel intrauterine system (LNG-IUS) in conservative treatment for patients with early-stage endometrial cancer and atypical hyperplasia. J Gynecol Oncol. 2019;30(4):e79.
26. Luo L, Luo B, Zheng Y, Zhang H, Li J, Sidell N. Oral and intrauterine progestogens for atypical endometrial hyperplasia. Cochrane Database Syst Rev. 2018;12:CD009458.
27. Abu Hashim H, Ghayaty E, El Rakhawy M. Levonorgestrel-releasing intrauterine system vs oral progestins for non-atypical endometrial hyperplasia: a systematic review and metaanalysis of randomized trials. Am J Obstet Gynecol. 2015 Oct;213(4):469–78.
28. Pal N, Broaddus RR, Urbauer DL, Balakrishnan N, Milbourne A, Schmeler KM, et al. Treatment of low-risk endometrial cancer and complex atypical hyperplasia with the levonorgestrel-releasing intrauterine device. Obstet Gynecol. 2018;131(1):109–16.
29. Leone Roberti Maggiore U, Martinelli F, Dondi G, Bogani G, Chiappa V, Evangelista MT, et al. Efficacy and fertility outcomes of levonorgestrel-releasing intra-uterine system treatment for patients with atypical complex hyperplasia or endometrial cancer: a retrospective study. J Gynecol Oncol. 2019;30(4):e57.
30. Minig L, Franchi D, Boveri S, et al. Progestin intrauterine device and GnRH analogue for uterus-sparing treatment of endometrial precancers and well-differentiated early endometrial carcinoma in young women. Ann Oncol. 2011;22:643–9.
31. Mazzon I, Corrado G, Masciullo V, Morricone D, Ferrandina G, Scambia G. Conservative surgical management of stage IA endometrial carcinoma for fertility preservation. Fertil Steril. 2010;93:1286–9.
32. Casadio P, Guasina F, Talamo MR, Paradisi R, Morra C, Magnarelli G, et al. Conservative hysteroscopic treatment of stage I well differentiated endometrial cancer in patients with high surgical risk: a pilot study. J Gynecol Oncol. 2019;30(4):e62.

33. Alonso S, Castellanos T, Lapuente F, Chiva L. Hysteroscopic surgery for conservative management in endometrial cancer: a review of the literature. Ecancermedicalscience. 2015;9:505.
34. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO-ESGO-ESTRO endometrial consensus conference working group. ESMO-ESGO-ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Radiother Oncol. 2015 Dec;117(3):559–81.
35. Arora V, Quinn MA. Endometrial cancer. Best Pract Res Clin Obstet Gynaecol. 2012;26(3):311–24.
36. 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;25:2798–803.
37. 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;125:477.
38. Gallos ID, Yap J, Rajkhowa M, Luesley DM, Coomarasamy A, Gupta JK. Regression, relapse, and live birth rates with fertility-sparing therapy for endometrial cancer and atypical complex endometrial hyperplasia: a systematic review and metaanalysis. Am J Obstet Gynecol. 2012;207(4):266.e1–12.
39. Park JY, Lee SH, Seong SJ, Kim DY, Kim TJ, Kim JW, 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.
40. Peiretti M, Congiu F, Ricciardi E, Maniglio P, Mais V, Angioni S. Conservative treatment for well-differentiated endometrial cancer: when and why it should be considered in young women. Ecancermedicalscience. 2019;13:892.
41. Zaino R, Whitney C, Brady MF, et al. Simultaneously detected endometrial and ovarian carcinomas: a prospective clinicopathologic study of 74 cases: a gynecologic oncology group study. Gynecol Oncol. 2001;83:355–62.
42. Richter CE, Qian B, Martel M, et al. Ovarian preservation and staging in reproductive-age endometrial cancer patients. Gynecol Oncol. 2009;114:99–104.
43. Wright JD, Buck AM, Shah M, Burker WM, Schiff PR, Herzog TJ. Safety of ovarian preservation in premenopausal women with endometrial cancer. J Clin Oncol. 2009;27:1214–9.
44. Elizur SE, Beiner ME, Korach J, Weiser A, Ben-Baruch G, Dor J. Outcome of in vitro fertilization treatment in infertile women conservatively treated for endometrial adenocarcinoma. Fertil Steril. 2007;88:1562–7.
45. Tong XM, Lin XN, Jiang HF, Jiang LY, Zhang SY, Liang FB. Fertility-preserving treatment and pregnancy outcomes in the early stage of endometrial carcinoma. Chin Med J. 2013;126(15):2965–71.
46. Yamagami W, Susumu N, Ichikawa Y, et al. Thirty-four successful cases of pregnancy following fertility-preserving hormonal therapy for endometrial cancer. Gynecol Oncol. 2012;125:S5.

MicroRNAs: Role in Cancer and miRNA Signatures in Endometrial Cancer

11

Heena Gautam, Manikankana Bandopadhyay, Sumita Mehta, and Mausumi Bharadwaj

11.1 Introduction

Cancer has affected both sexes almost equally in the year 2018 with incidences of 9 million in males and 8.5 million in females. The world cancer data 2018 by Globocan reported approximately 382,069 women diagnosed with endometrial cancer (EC) in 2018 and 89,929 women that died due to the disease in the year; the age-adjusted annual incidence being 14.14 per 100,000 women. The estimated new cases in India were 13,328 and the estimated deaths were around 5010 [1]. NCI (National Cancer Institute) data from 2014 to 2016 reports that approximately 3% of women will be diagnosed with EC at some point in their lifetime.

Earlier EC was considered to be the disease of the developed world but now the concern for the disease is gaining as this disease is found to be drastically increasing in the developing world as well. EC is mainly a disease of the post-menopausal women more than 55 years of age and is rarely found in women under the age of 45 years, but recently considerable percentage of women aged below 45 years are diagnosed with the disease for which the risk factors are still unclear and need to be explored further. Despite the advances in therapeutic techniques such as radiotherapy, chemotherapy, or surgery in recent years,

H. Gautam · M. Bandopadhyay · M. Bharadwaj (✉)
Division of Molecular Genetics and Biochemistry, Indian Council of Medical Research (ICMR), National Institute of Cancer Prevention and Research, Noida, Uttar Pradesh, India
e-mail: mausumi.bharadwaj@gov.in

S. Mehta
Department of Obstetrics & Gynecology, Babu Jagjivan Ram Memorial Hospital, New Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_11

the rate of survival in EC patients remains unsatisfactory and there is still an unmet need for the best opportunity to cure the women suffering from EC. Expression of specific microRNAs (miRNA) may allow early detection of cancer as well as help in planning treatment strategies. MicroRNAs are 19–23 base pair long functional transcripts that regulate gene expression by cleavage or translational suppression of target mRNA. Till date, over 2000 mature human miRNAs are known and it is estimated that approximately 60% of human mRNA could be targets of miRNA. Depending on the target gene sequence, the mature miRNA either stimulates the repression of translational mechanisms or persuades mRNA degradation. Hence, these molecular features of miRNA can be incorporated for better assessment of the biological behavior of an individual's disease as well as in planning improved treatment strategies. Widespread differential expressions of miRNA genes in malignant tissues across many cancer types compared to normal tissues are now well documented. There is considerable evidence to indicate that miRNAs and their biogenesis machinery are involved in the development of cancer by both oncogenic and tumor-suppressive roles. A single miRNA can target a number of mRNAs whereas one mRNA can be a target of more than one miRNA. Exosomes released from endometrial epithelial cells are a vital factor as an attractive source of biomarkers, through the analysis of the inner cargo of specific mRNA and miRNA by qRT-PCR. miRNA-based therapeutics can be divided into miRNA mimics and inhibitors of miRNAs. There are different types of delivery systems for miRNA mimics in vivo such as viral vectors, neutral lipid emulsions, dendrimers, cyclodextrin, and chitosan. Herein, we describe the role of miRNAs in cancer biology and how their genomic interaction will impact both research and clinical management for EC.

11.2 Endometrial Cancer

An increase in obesity, young age at menarche, and a decline in fertility rate have increased the incidence of endometrial cancer and made it to be a substantial health concern around the globe [2].

EC is mainly diagnosed among the postmenopausal women in the age group of more than 55 years and it is generally considered a rare event in women under the age of 45 years. Recently there has been a trend in women that may reveal patterns for future risk of EC in premenopausal or perimenopausal women aged 30–54 years for which the risk factors are still unclear and need to be explored further [3]. A Korean study observed EC in 37.1% women who were in their 50s and 25.6% of cases were observed in women in their 40s [4]. Despite the advances in therapeutic modalities of radiotherapy, chemotherapy, or surgery in recent years, the rate of survival in EC patients remains unsatisfactory with 5-year

survival rates for women with stage III and stage IV being 60% and 20%, respectively [5, 6].

11.3 MicroRNA (miRNA)

MicroRNAs (miRNAs) are 19–23 base pair long functional transcripts that regulate gene expression by cleavage or translational suppression of target mRNA. The miRNAs were discovered in 1993 [7]. These small noncoding RNAs play major roles in the modulation of gene expression by pairing with the 3′-untranslated regions (UTRs) of target transcripts. Till date, over 2000 mature human miRNAs are known and in silico prediction estimates that approximately 60% of human mRNA could be targets of miRNA. If there is a partial complementarity between the miRNA and target mRNA, it brings about the repression of translation, whereas if both are perfectly complementary, it causes degradation of the target mRNA.

11.4 Genomics, Biogenesis, and Functions of miRNAs

Most miRNA genes come from regions of the genome relatively distant from previously marked genes, indicating that they derive from independent transcription units. Nevertheless, a substantial minority (e.g., about a quarter of the human miRNA genes) are in the introns of pre-mRNAs. These are preferentially in the same orientation as the predicted mRNAs, signifying that most of these miRNAs are not transcribed from their own promoters but are rather processed from the introns as observed for many small nuclear RNAs (snoRNAs) also. The miRNAs within a genomic cluster are regularly, though not always, linked to each other; and miRNAs are sometimes but not always clustered. This arrangement offers an appropriate mechanism for the synchronized expression of a miRNA and a protein [8].

11.4.1 Biogenesis of miRNAs

The biogenesis of miRNAs is a complex process involving several steps. In brief, the first primary miRNAs (pri-miRNAs) are transcribed by RNA polymerase II and III in the nucleus. They are excised subsequently by the ribonuclease Drosha-DGCR8 complex to produce approximately 60–70 nucleotide stem loop intermediate known as precursor miRNAs (pre-miRNAs) in the nucleus. These pre-miRNAs are then transported to the cytoplasm by Ran-GTP and the export receptor exportin-5. In the cytoplasm they are excised by the RNAse III enzyme called Dicer, leading

to the production of a miRNA duplex. This duplex sequentially splits in order to create the single-stranded mature miRNA that finally forms the RNA-induced silencing complex (RISC). RISC and Argonaute/EIF2C (AGO) proteins together facilitate the target-mRNA recognition.

Identification of target mRNA by miRNA occurs through specific base-pairing interactions between the 5′ end (seed sequence) of miRNA and sites within coding and untranslated regions (UTRs), particularly 3′-UTR of mRNAs. Finally, depending on the target gene sequence, the mature miRNA either stimulates the repression of translational mechanisms or persuades mRNA degradation. In other words, if the miRNA and target mRNA are not completely complementary to each other, it will result in the repression of translation, whereas if they are perfectly complementary, it will lead to degradation of the target mRNA [9]. After the cleavage of the mRNA, the miRNA remains intact and governs the recognition and degradation of additional messages. Suppression of protein synthesis occurs by blocking the initiation of translation at the cap recognition or inducing ribosomes to drop off prematurely. An alternative possibility of translational repression is proposed as translation continues at the same rate but results in nonproductive protein as the newly synthesized polypeptides are immediately degraded. However, it is better to consider these two possibilities under the same umbrella as translational repression. The mature miRNA can also augment the expression of the target genes, even under circumstances of growth arrest in the cell [10]. Interestingly, it has been recently reported that miRNA can interact with ribonucleoprotein or directly bind to DNA and establish transcriptional silencing in a RISC-independent manner.

11.5 Role of miRNA in Cancer

Presently, ~2000 microRNAs have been identified in humans. A single miRNA may regulate many mRNAs; similarly, a single mRNA may be targeted by many miRNAs, establishing miRNAs as the largest class of gene regulators. Through this mechanism, microRNAs are an essential component to regulating most cellular, developmental, physiological, and pathological processes, including organ development, differentiation, proliferation, immune regulation functions including immune response, apoptosis and tumorigenesis [11]. Hence, it is of no surprise that miRNAs are involved in cancer development and progression. Depending upon their target gene and level of expression, microRNAs may function as either tumor suppressors or oncogenes and help in the promotion or suppression of cancer growth and progression. The involvement of miRNAs is being uncovered in almost all aspects of cancer biology, such as proliferation, tumorigenesis, apoptosis, invasion/metastasis, and angiogenesis [11]. These small RNAs coordinate the interplay between complex signal transduction pathways. Widespread differential expressions of miRNA genes in malignant tissues across many cancer types compared to normal tissues are now well documented.

11.5.1 Deregulation of miRNA Biogenesis Enzymes

There is considerable evidence to indicate that miRNAs and their biogenesis machinery are involved in the development of cancer. The miRNA biogenesis proteins Drosha and Dicer are downregulated in several cancer types and this downregulation has been associated with poor patient outcomes.

Drosha expression is regulated by oncogenic transcription factors such as MYC25 or the RNA-specific deaminase ADARB1, leading to decreased primary miRNA (pri-miRNA) processing [12, 13]. Drosha was also reported to be downregulated in response to tumor hypoxia, and this process was mediated by the direct binding of the hypoxia-responsive transcription factors ETS1 and ELK1 to the promoter of Drosha.

The mechanisms of Dicer downregulation in cancer are greatly diverse. For example, Dicer downregulation can be due to the loss or downregulation of the transcription factor TAp63, which is a frequent occurrence in cancer. TAp63 normally activates DICER expression by directly binding to its promoter. Dicer can also be downregulated through direct targeting of the 3′ UTR region of Dicer by miRNAs such as miR-103/107, let-7 and miR-630, with tumor hypoxia further influencing these effects. Downregulation of Dicer expression by epigenetic mechanisms, which are mediated by the hypoxia-induced inhibition of the oxygen-dependent tri-methylated histone H3 lysine 27 (H3K27me3) demethylases KDM6A and KDM6B34, is an example of such event.

The miRNA biogenesis protein AGO2 can be inhibited by epidermal growth factor receptor (EGFR)-dependent phosphorylation in cancer. Breast cancer cells exposed to hypoxia have an increased association between EGFR and AGO2, leading to the phosphorylation of AGO2 at the Y393 residue. This process results in decreased AGO2 binding to Dicer, functionally resulting in increased cancer cell survival and invasiveness. Furthermore, mutations in the gene encoding exportin-5 crucially involved in decreasing the cytosolic export of miRNAs in cancer. This effect results in the increased expression of oncogenes such as EZH2 and MYC as a result of suppressed expression of the miRNAs.

In addition to the direct deregulation of miRNA biogenesis, the DNA damage response in cancer cells can lead to increased processing of selected sets of miRNAs. This effect is due to the ATM kinase-dependent phosphorylation of KH-type splicing regulatory protein (KSRP), which results in the binding of KSRP to pri-miRNAs and their subsequent preferential processing. Though the functional effects of such preferential processing remain unclear, we speculate that a decrease in such preferential processing may increase tumorigenesis due to the loss of tumor suppressor miRNAs based on the observation of downregulation of KSRP in cancers [14].

11.5.2 Deregulation of Tumor-Suppressive miRNAs

miRNA expression analyses have suggested both oncogenic and tumor-suppressive roles of miRNAs. A single miRNA can target a number of mRNAs whereas one

Table 11.1 Selected tumor suppressor miRNAs and their significant targets

miRNAs	Chromosomal location	Diseases	Significant mRNA targets
let-7 family	Please see Table 11.2	• Solid tumors (e.g., breast, colon, ovarian, lung, liver, and glioma) • B cell lymphoma	MYC, BCLXL, pan-RAS, EZH2, HMGA2, FAS, P21, PGRMC1, and DICER1
miR-34a	1p36.22	• Solid tumors (e.g., lung, liver, colon, brain, prostate, pancreatic, bladder, and cervical) • Myeloma • B cell lymphoma	BCL2, MET, MYC, CDK6, CD44, SRC, E2F1, JAG1, FOXP1, PDGFRA, PDL1, and SIRT1
miR-143		• Solid tumors (e.g., bladder, lung, breast, colon, pancreas, cervical, and head and neck) • Lymphoid leukemia	KRAS, ERK5, VEGF, NFKB1, MYC, MMPs, PLK1, CDH2, and EGFR
miR-145	5q32		
miR-200 family	1p36.33	Solid tumors (e.g., breast, ovarian, and lung)	ZEB1, ZEB2, BMI1, SUZ12, JAG1, SOX2, SP1, CDH1, and KRAS
miR-15/16	13q14	• Solid tumors (such as bladder cancer, colon cancer, and melanoma) • Chronic lymphocytic leukemia	BCL-2, CDC2 (also known as CDK1), ETS1, and JUN

mRNA can be a target of more than one miRNAs. There are certain miRNAs that can target oncogenic mRNAs and thereby suppress or reduce their oncogenic function. These miRNAs are designated as tumor-suppressive miRNA. The miR-34 family, miR-200 family, let-7family of miRNAs, miR-15/16 are the examples of such tumor-suppressive miRNAs [14]. If the expression of such tumor-suppressive miRNAs are downregulated, as a consequence, expression of oncogenes increases thereby leading to escalation of the process of tumorigenesis. Tables 11.1 and 11.2 describe selected tumor suppressor miRNAs and their involvement in various types of cancer.

11.5.3 Deregulation of miRNAs Oncogenic Function

Studies have shown that many miRNAs exhibit transcriptional upregulation and consequently increased expression during different malignancies. Few of them are miR-21 (known to have antiapoptotic function and often activated by transcription factor AP-1 and cytokine TGF-β), miR-155 (known to modulate many genes that are involved in cell homeostasis, angiogenesis, and cancer cell survival), miR-210 (downregulates the AIFM thereby promoting survival of cancer cells and ephrinA3,

Table 11.2 Chromosomal location of let-7 family

let-7 Family	Genome context	Clusters
hsa-let-7a-2	chr11: 122146522-122146593 –	Cluster1-a (*let-7a-2*, *miR-100*, *miR-125b-1*)
hsa-let-7c	chr21: 16539828-16539911 +	Cluster1-b (*let-7c*, *miR-99a*, *miR-125b-2*)
hsa-let-7e	chr19: 51692786-51692864 +	Cluster1-c (*let-7e*, *miR-99b*, *miR-125a*)
hsa-let-7a-1	chr9: 94175957-94176036 +	Cluster2 (*let-7a-1*, *-7d*, *-7f-1*)
hsa-let-7d	chr9: 94178834-94178920 +	
hsa-let-7f-1	chr9: 94176347-94176433 +	
hsa-let-7a-3	chr22: 46112749-46112822 +	Cluster3 (*let-7a-3*, *-7b*)
hsa-let-7b	chr22: 46113686-46113768 +	
hsa-let-7f-2	chrX: 53557192-53557274 –	Cluster4 (let-7f-2, miR-98)
hsa-miR-98	chrX: 53556223-53556341 –	
hsa-let-7g	chr3: 52268278-52268361 –	
hsa-let-7i	chr12: 62603686-62603769 +	

leading to increased tumor angiogenesis), miR-17~92 cluster (downregulates cell cycle regulator E2F1 thereby facilitating cell proliferation, pro-apoptotic protein BIM resulting in decreased apoptosis of B lymphocytes, antiangiogenic factors thrombospondin 1 (TSP1) and connective tissue growth factor (CTGF)), miR-221 (known to target several tumor suppressor genes viz. p27, PTEN, TIMP3 and DNA damage-inducible transcript 4 (DDIT4)) [14]. Table 11.3 depicts selected miRNA with oncogenic potential and their involvement in different malignancies.

11.5.4 Intercellular Communication by Exosome-Derived miRNA in Cancer

The transport of mRNAs and miRNAs by exosomes was realized only recently but has led to an explosion of interest in cancer research. Exosomes (approximately 100 nm nanovesicles) are membrane-derived vesicles that have recently been recognized as important mediators of intercellular communication, as they carry lipids, proteins, mRNAs, and miRNAs that can be transferred to a recipient cell via fusion of the exosome with the target cell membrane. In the context of cancer cells, this process involves the transfer of cancer-promoting cellular contents to surrounding cells within the tumor microenvironment or into the circulation to act at distant sites, thereby enabling cancer progression. Exosomes released from endometrial epithelial cells are a vital factor of these interactions. Exosomes not only are secreted from tumor cells, but endometrial cancer cells can transmit small regulatory RNAs to endometrial fibroblasts via exosomes. Isolated exosomes could become an attractive source of biomarkers, through the analysis of the inner cargo of specific mRNA and miRNA by qRT-PCR from uterine aspirates.

Table 11.3 Selected oncogenic miRNAs and their significant targets

miRNAs	Chromosomal location	Diseases	Significant mRNA targets
miR-10b	2q31.1	Solid tumors (e.g., breast and glioma)	NF1, CDH1, E2F1, PIK3CA, ZEB1, and HOXD10
miR-155	21q21.3	• Solid tumors (e.g., liver, lung, kidney, glioma, and pancreas) • B cell lymphoma • Lymphoid leukemia	SHIP, SPI1, HDAC4, RHOA, SOCS1, BCL2, JMJD1A, SOX6, SMAD2, SMAD5, and TP53INP1
miR-221 miR-222	Xp11.3	Solid tumors (e.g., liver, pancreas, and lung)	CDKN1B, CDKN1C, BMF, RB1, WEE1, APAF1, ANXA1, and CTCF
miR-21	17q23.2	• Malignant B cell lymphoma • NSCLC • Lung adenocarcinoma	SMAD7, PDCD4, RECK, PTEN
miR-17~92 cluster	13q31.3	Solid tumors (e.g., liver, colon)	MIR17HG, E2F1, BIM, TSP1, CTGF

11.5.5 Aberrant Epigenetic Regulation

Alterations in miRNAs can cause abnormal epigenetic patterns which can further lead to deregulation of critical genes involved in cell proliferation, apoptosis, and cell differentiation. Evidence has shown that miRNAs can be deregulated by abnormal CpGs methylation and/or histone modifications. Conversely, many miRNAs play an active role in effecting gene expression and creating highly controlled feedback circuits. This subgroup of miRNAs is called "epi-miRNAs" [15].

miRNAs act as epigenetic regulators by:

- Posttranscriptional gene silencing: miRNAs cause deregulation of proteins such as heterochromatin protein (HP1), PRC1, and PRC2 at the posttranscriptional level leading to the epigenetic silencing of tumor suppressor genes. miR-29 family, for example, downregulates DNA methyltransferase in lung cancer thereby resulting in a decrease in global DNA methylation [16].
- Regulate gene transcription: miRNAs regulate gene transcription either through transcriptional gene silencing or gene activation. miRNA-320 was the first miRNA to be identified as a repressor of gene transcription. It was responsible for silencing of the POLR3D gene whose abnormal activity is characteristic of cancer cells [17]. miRNAs also activate the target gene promoter and induce gene expression. miRNA-373 was the first one to be discovered as being able to cause gene activation. It induces the expression of tumor suppressor gene CDH1 in prostate cancer cells [18].

11.6 miRNA in Therapeutics

miRNA-based therapeutics can be divided into miRNA mimics and inhibitors of miRNAs (also known as anti-miRs). miRNA mimics are synthetic double-stranded small RNA molecules that match the corresponding miRNA sequence and therefore functionally aim to replace the lost miRNA expression. By contrast, anti-miRs are single-stranded and antisense oligonucleotides (ASOs), which are planned to target mRNAs, or are modified with locked nucleic acids (LNAs). Anti-miRs with a 2′-*O*-methoxyethyl modification are also termed AS antagomiRs. These synthetic small RNA molecules have a complementary sequence to the miRNA to be inhibited and block the function of the corresponding miRNA by binding to it strongly. In the course of time, significant improvements in binding affinity, stability, and target modulation effects of miRNA mimics and anti-miRs have been attained through chemical modifications to the nucleotide backbone.

One of the challenges for RNA-based therapeutics (including single- or double-stranded oligonucleotides) is the possibility for degradation of oligonucleotides by RNases in serum or in the endocytic compartment of cells. To avoid this issue, two different strategies have been investigated:

1. To alter oligonucleotide structure by modifying the nucleotides or the RNA backbone through methylation or LNAs, or by adding phosphorothioate-like groups.
2. To develop delivery vehicles to encapsulate RNAs for protection and to allow endosomal escape. Currently available commercial miRNA mimics are often modified by methylation of the passenger strand for increased stability, and anti-miRs are modified using LNA chemistry.

11.6.1 Alteration of Oligonucleotide Structure

- Antisense oligonucleotides (ASOs)

  First-generation ASOs were altered by substituting the non-bridging oxygen in the phosphate group with sulfur, thereby producing phosphorothioate nucleotides. This modification increases the stability of ASOs inside cells (by making internucleotide linkages resistant to nucleases degradation) while retaining sufficient RNase H activity for the cleavage of target mRNA and function in suppressing target gene expression. Additional modifications of ASOs include the addition of methyl groups at different locations in the RNA backbone. The addition of a 2′-*O*-methyl group to phosphorothioate nucleotides results in increased binding affinity to target mRNA, significant nuclease resistance, and higher in vivo stability. A 2′-*O*-methoxyethyl modification also enhanced nuclease resistance and binding affinity [19].

- Anti-miRs

  Anti-miRs are structurally similar to ASOs but anti-miRs bind directly to the mature strand of the targeted miRNA and thus induce a functional blockage. Currently different types of modifications of anti-miRs are being used that had previously been developed for ASOs. For example, an anti-miR with a 2′-*O*-methoxyethyl modification against miR-122 resulted in improved target modulation compared with unmodified anti-miRs. Furthermore, LNA-modified anti-miRs have been proved significantly advanced in the oligonucleotide chemistry. LNA-modified anti-miRs are chemically locked by a bridge that connects the 2′-oxygen and 4′-carbon in a ribonucleotide, mimicking C3′-endoconformation. To enhance the efficacy of miRNA targeting, repeated patterns of two deoxyribonucleotides, followed by one locked ribonucleotide (called LNA "mixmers") have been designed. These "mixmers" showed promising results in vivo in mouse models of cancer, cardiac disease and diabetes, and in nonhuman primates also.

11.6.2 Delivery Systems for miRNA Therapeutics

Chemical modifications of miRNA mimics to enhance the stability under in vivo conditions have one major limitation that is the loss of mRNA silencing ability. This loss of efficiency is due to the loading of the miRNA into the RNA-induced silencing complex (RISC). This limitation has led to the development of alternative approaches to increase the efficacy of in vivo delivery, such as encapsulating the miRNA mimic into nanoparticles. Considering the similarity between miRNA mimics and small interfering RNA (siRNA) structure and functions (both are double-stranded small RNA molecules), different delivery systems are being tried and some of them are now in late-stage clinical trials. Different types of delivery systems are discussed below:

- Viral vectors**:** Adenovirus vectors that encode small RNA molecules of interest have been constructed. Limitations are the safety issues to apply this method in practice.
- Neutral lipid emulsions**:** Among the lipid-based delivery systems, neutral lipid emulsions (NLEs) constitute a significant proportion of tested vehicles. NLEs comprise of 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), squalene oil, polysorbate 20, and an antioxidant. NLEs are neutral charge nanoparticles with low toxicity. Limitations are with regard to the efficiency of delivery to tumor sites.
- Neutral liposome 1,2-dioleoyl-sn-glycero-3-phosphatidylcholine: DOPC-based nanoparticles have been widely used in the preclinical setting for the delivery of siRNAs and have advanced to phase I trials for siRNA-based approaches. These nanoparticles have been tested in preclinical studies to deliver miRNA mimics.
- Poly(lactide-co-glycolide) particles**:** Poly(lactide-co-glycolide) (PLGA) is a polymer that is widely used for the delivery of small RNAs in vivo. PLGA has low toxicity owing to its neutral charge, and the delivery rate of RNA molecules

can be controlled by altering the composition of the PLGA particles. PLGA has been used in the clinic for biodegradable sutures, and it has a high safety profile. Limitations are the low rates of siRNA or miRNA loading.

- EnGeneIC Delivery Vehicle nanocells**:** EnGeneIC Delivery Vehicle (EDV) nanocells (also called TargomiRs) are bacterium-derived 400 nm particles that had earlier been shown to have the capacity to deliver chemotherapeutic agents and have been modified with surface-conjugated antibodies to enable specific targeting of disease sites.
- Synthetic polyethylenimine**:** Polyethylenimine (PEI) is one of the early-generation polymers studied for nucleic acid delivery 178. Upon forming a complex with nucleic acids, PEI retains a small positive charge, which allows it to adhere to the negatively charged cell membrane and undergo endocytosis.
- Dendrimers: Dendrimers consist of poly(amidoamine)- or poly(propylenimine)-conjugated nucleic acids. These molecules have shown a high efficiency in delivering nucleic acids such as siRNAs in mouse studies; however, due to their cationic charge, they are often connected with toxicity.
- Cyclodextrin**:** This glucose polymer has been widely used in medical formulations 180. The first clinical trial of a siRNA therapeutic used was cyclodextrin-based delivery. Significant mRNA target engagement was shown. Limitations are dose-limiting toxicity seen with it.
- Polyethylene glycol (PEG): One of the most advanced siRNA delivery systems in clinical trials in recent days is based on polyethylene (PEG)–siRNA conjugates. Here nucleic acids are conjugated to PEG via a disulfide linkage. These particles showed superior gene-silencing efficacy compared with the PEI system. These conjugates were further modified by linkage to cyclodextrin, and the resulting molecules were used in the first clinical trial involving siRNAs.
- Chitosan**:** Chitosan is a cationic polymer obtained from chitin (a naturally occurring polysaccharide composed of glucosamine and *N*-acetylglucosamine residues). It has been extensively used for the delivery of siRNAs in preclinical studies. Owing to their biodegradability and low cellular toxicity, chitosan–nucleic acid conjugates provide an effective system for delivering miRNAs.
- *N*-acetyl-D-galactosamine: siRNAs or miRNA mimics can be conjugated to *N*-acetyl-D-galactosamine (GalNAc), which leads to their uptake into cells by clathrin-mediated endocytosis. GalNAc–siRNA conjugates—namely ALN-PCSsc (Alnylam Pharmaceuticals), and GalNAc–miRNA conjugates—such as RG-101 (Regulus), are currently being evaluated in phase I and phase II trials. An advantage of GalNAc conjugates is that they can be delivered without the need of additional delivery carrier molecules such as lipids. GalNAc–siRNA conjugates can efficiently accumulate in the liver due to their high affinity for the asialoglycoprotein receptor. Limitations are very narrow and restricted use of GalNAc chemistry beyond hepatocytes related altered gene diseases.

11.7 Expression Profile of miRNA in EC

Current research aims to detect and characterize new biomarkers for a better understanding of the different subtypes of EC, to provide an improved assessment of prognosis, and for optimization of patient care. microRNAs are emerging as attractive candidates for biomarkers. Extracellular vesicles (EVs) containing proteins, lipids, and nucleic acid (DNA/RNAs) involved in intercellular communication are considered as useful forms of liquid biopsy [20]. Among them, miRNAs are steadily and frequently found in human serum and are protected from RNAase-mediated degradation in body fluids. As a result, they have emerged as candidate biomarkers for many types of diseases. Nowadays, circulating miRNAs have been exploited as diagnostic and prognostic biomarkers in the pathological development of cancer. For diagnostic purposes, circulating miRNAs (particularly in plasma/serum) have appeared as an important source of clinical material.

Various studies have shown that in EC, miRNA expression pattern appears to be associated with certain prognostic factors such as lymph node involvement, lymphovascular space invasion (LVSI), overall survival (OS), and recurrence-free survival (RFS) [21].

Torres et al. for the first time studied microRNA expression in plasma samples of EC patients. They found increased expression levels of miR-99a, miR-100, and miR-199b in plasma samples from patients when compared with healthy controls. The combined analysis for plasma miR-99a/miR-199b resulted in 88% sensitivity and 93% specificity discriminating patients versus controls, indicating a good diagnostic potential [22]. Various other miRNAs are upregulated in EC and are responsible for oncogenesis, invasion, and metastasis. The common miRNAs upregulated include miR-185, miR-106a, miR-181a, miR-423, and miR-107 [23–25]. Upregulation of miR-27, which is surgical stage-dependent, causes reduced expression of FOXO1, a target gene of miR-27 that inhibits apoptosis [26]. A more recent study analyzed 16 miRNAs in plasma of 34 EC patients and 14 controls, finding miR-9/miR-1228 and miR-9/miR-92a as a good signature for use as a diagnostic tool (Area Under Curve, AUC values ~0.9). After a genome-wide serum miRNA expression analysis, miR-222, miR-223, miR-186, and miR-204 were found upregulated and identified as a powerful signature for EC detection (AUC of 0.927).

In the study conducted by Dai et al., overexpression of miR-200b inhibited expression of tissue inhibitor of metalloproteinase-2 and increased levels of matrix metalloproteinase and thus concluded that miR-200 is involved in metastasis of endometrial cancer [27]. Hiroki et al. found miR-34b to be involved in proliferation and invasion of endometrial cancer [28].

In contrast, many miRNAs are downregulated in EC; these include miR-30c, miR-221, miR-152, miR-193b, and miR-204 [23, 24]. More recently, in a meta-analysis including EC patients, it was demonstrated that serum miR-21 could serve as a novel biomarker for EC. Interestingly, in addition to serum and plasma samples, urinary miRNAs can be explored in patients with EC, finding a specific downregulation of miR-106b in comparison with healthy donors. All these results point toward a great potential of miRNA signatures in EC, although until now there is no consistent and clinically validated signature of miRNAs in the management of EC.

miRNAs also play a role in the progression of endometrial cancer through DNA methylation. miR-152 expression is regulated by methylation and is downregulated in endometrial cancer. By inhibiting the expression of DNA methyltransferase, met proto-oncogene and rapamycin-insensitive companion of mTOR, it inhibits oncogenesis [29]. Let-7a decreases levels of Aurora-B protein and causes inhibition of EC onset [30]. Downregulation of miR-30leads to overexpression of FOXC1 promoting invasion and metastasis [31]. miR-30c regulates metastasis-associated gene (MTA1) and its downregulation may be involved in type I and II EC [32]. Estradiol also downregulates miR-30 thereby establishing its role in the oncogenesis of endometrial cancer [33].

Improved information on the expression profile of miRNAs would likely elucidate certain molecular mechanisms associated with EC and could provide the platform for diagnostic tests, prognosis, or the identification of potential novel therapeutic targets. Table 11.4 depicts the association of various miRNAs with the prognosis of endometrial cancer.

Table 11.4 miRNA expression profile in endometrial cancer

Expression profile of miRNAs	miRNA with increased expression	miRNA with decreased expression
Associated with malignant endometrial tissues compared to healthy or hyperplastic endometrial tissues	miR-9, -9∗, -9-3p, -10a, -18a-3p, -19b, -25-5p, -27a, -31,-34a, -95, -96, -103, -106a, -106b, -107, -130b, -135a, -135b, -141, -142-5p, -146, -146b-5p, -151, -153, -155, -181a, 181c-3p, -181c, -182, -183,-184, -191, -193-3p, -194, -200a, -200a∗, -200a-5p, -200b, -200b∗, -200c, -203, -205, -210, -215, -221, -223, -218, -301, -325, -326, -330, -337, -363, -423, -425, -429, -432, -449, -499, -518d-5p, -520c-5p, -522, -526a, -1202, -5787, and -miR-6749-5p	miR-10b, -10b∗ -21, -23a∗, -29c, -30a-3p, -30a-5p,-30c, -31, -32, -33b, -99a, -99a-3p, -99b, -100, -101, -126, -127-3p, -133b, -139-5p, -152, -185, -193, -193a,-193b, -195, -196a, -196a-5p, -199b, -199b-3p, -199b-5p, -204, -214, -216b, -221, -302a-5p, -328-3p, -337-3p, -338-3p, -367-3p, -368, -369, -370, -376a, -376c, -377, -377-5p, -381, -409, -410, -411,-424, -424∗, -424-3p, -431, -432, -449a, -451, -487b, -496, -503, -516, -542-3p, -542-5p, -596, -610, -630, -632, -652,-758, -760, and miR-1247
According to Lymph Node Status	miR-10a, -10b, -26a, -26a1, -34a, -95, -123, -125b1, -125b2, -133a, -143, -145a, -181a, -200a∗, -203, -222-3p, and miR-429.	miR-24b-5p, 34c-3p, -34c-5p, -184, -204-5p, and miR-375
According to Survival	miR-10b∗, -29b, -100, -101, -129-2, -130b, -139-5p, -152, -183-5p, -194, -199a-5p, -202, and miR-455-5p	miR-200c, -205, -429, and -1228 and of the combined expression of six miRs (miR-15a, miR-142-3p, miR-142-5P, miR-3170, miR-1976, miR-146a)
Specific miRNAs in the Plasma/Serum in the Presence of Endometrial Cancer	miR-15b, -27a, -92a, -99a, -100, -135b, -141, -143, -186, -199b, -200a, -203, -204, -205, -222, -223, -449a, -1228, and miR-1290	miR-9, -21, -30a-3p, -204, -301b, -1179, -3145-5p, -4502, -4638-3p, and miR-4665-5p

11.8 Clinical Implications of miRNA in EC

11.8.1 miRNA as a Biomarker

miRNAs are useful as biomarkers as particular carcinomas have specific miRNAs expression profiles. They can be used as markers not only for early diagnosis but also for prognosis. Tan et al. in his study found an association between the upregulation of miR-155 and cancer stage and metastasis [34]. Endometriosis which is a precursor for EC can be diagnosed early using miR-199a and miR-542-3p as biomarkers with a sensitivity of 96.6% and specificity of 79.6%, respectively [35]. Montagnana M et al. found that a combination of miRNAs, miR-222, miR-223, miR-186, and miR-204 can diagnose endometrial carcinoma with high accuracy with an area under ROC curve of 0.927. They even found the diagnostic performance of miRNAs to be better than that of Ca-125. miR-205 which targets PTEN is seen to be associated with decreased survival [36].

miRNAs can also be used to diagnose type II EC which has no precancerous phase and arises de novo. There is significant upregulation of miR-125b in type II endometrial cancer cells as compared to type I endometrial cells. V-erb-b2 erythroblastic leukemia viral oncogene homolog 2 (ERBB2), which is also the target of miR-125b, is involved in the invasion of cancer cells [37]. miR-194 correlates with the stage of cancer and may be used as a biomarker for prognostic diagnosis of endometrial cancer [38]. It targets the oncogene BMI1 and inhibits the EMT phenotype and EC cell invasion [39]. Type II endometrial cancer is frequently associated with KRAS mutation. miR-181b, miR-324-3p, and miR-518b which have been found to be downregulated in cancer with KRAS mutation can help as markers for Type II cancers. The KRAS-variant and miRNA expression in RTOG endometrial cancer clinical trials [40].

11.8.2 miRNAs for Treatment of EC

One of the most important dilemmas in the management of endometrial cancer is to establish a guideline for when to perform lymphadenectomy in the initial surgical management. Expression levels of miR-34 and miR-184 showed that a decrease in their levels was associated with positive lymph node status. Decreased expression of miR-34 in serous EC has been shown to be strongly associated with LVSI [41].

miRNAs themselves can be used for cancer treatment as a means of increasing expression of tumor suppressor genes and inhibiting oncogenes. Administration of a tumor suppressor miR, miR-152, in vitro and in vivo gave significant tumor suppression [42].

Drug sensitivity of cancer can also be influenced using miRNAs. Expression of miR-34c, which regulates metastasis, cell death, and invasion, is markedly downregulated in EC, and a combination of a miR-34c mimic with cisplatin improved the drug efficacy in cell lines [43]. Shen Y et al. showed that Bortezomib, which inhibits ubiquitin-dependent proteolysis thereby diminishing the proliferation and proteasomal activity of endometrial cells, acts by modulating miR-17-5p [44].

miR analysis of endometrial tumor tissue adds prognostic and therapeutic value to the management of endometrial cancer with certain miR expression profiles being associated with prognostic factors like lymph node status and LVSI. Research concerning possible therapeutic implications of miRNAs is still ongoing to improve the efficacy and minimize the unwanted effects of such therapy.

11.9 Key Points

1. Globocan (2018) reported approximately 382,069 women diagnosed with endometrial cancer (EC) in 2018 and 89,929 women that died due to the disease; the age-adjusted annual incidence being 14.14 per 100,000 women.
2. EC is mainly diagnosed among the postmenopausal women in the age group of more than 55 years; recently a considerable percentage of women aged below 45 years are diagnosed with the disease.
3. MicroRNAs (miRNAs) are 19–23 base pair long functional transcripts that regulate gene expression by cleavage or translational suppression of target mRNA.
4. There is considerable evidence to indicate that miRNAs and their biogenesis machinery are involved in the development of cancer by both oncogenic and tumor-suppressive roles.
5. Depending on the target gene sequence, the mature miRNA either stimulates the repression of translational mechanisms or persuades mRNA degradation.
6. The molecular features of miRNA can be incorporated for the better assessment of the biological behavior of an individual's disease and its risk involved for improved treatment, cure, and prevention.
7. Certain miR expression profiles are associated with prognostic factors like lymph node status and LVSI.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Parslov M, Lidegaard O, Klintorp S, Pedersen B, Jønsson L, Eriksen PS, Ottesen B. Risk factors among young women with endometrial cancer: a Danish case-control study. Am J Obstet Gynecol. 2000;182(1):23–9.
3. Hecht JL, Mutter GL. Molecular and pathologic aspects of endometrial carcinogenesis. J Clin Oncol. 2006;24(29):4783.
4. Rizzuto I, Nicholson R, MacNab WS, Nalam M, Sharma R, Rufford B. Risk factors and sonographic endometrial thickness as predictors of tumour stage and histological subtype of endometrial cancer. Gynecol Oncol Rep. 2019;30:100491.
5. Nemani D, Mitra N, Guo M, Lin L. Assessing the effects of lymphadenectomy and radiation therapy in patients with uterine carcinosarcoma: a SEER analysis. Gynecol Oncol. 2008;111(1):82–8.
6. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983; 15(1):10–7.

7. Lee RC, Feinbaum RL, Ambros V. The C. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell 1993; 75:843–54.
8. Lagos-Quintana M, Rauhut R, Meyer J, Borkhardt A, Tuschl T. New microRNAs from mouse and human. 2003; RNA 9:175–9.
9. Bartel DP. MicroRNAs: target recognition and regulatory functions. Cell. 2009;136:215–33.
10. Friedman RC, Farh KK, Burge CB, Bartel DP. Most mammalian mRNAs are conserved targets of microRNAs. Genome Res. 2009;19:92–105.
11. Hannafon BN, Ding W-Q. Intercellular communication by exosome-derived microRNAs in cancer. Int J Mol Sci. 2013;14:14240–69. https://doi.org/10.3390/ijms140714240.
12. Wang X, Zhao X, Gao P, Wu M. c-Myc modulates microRNA processing via the transcriptional regulation of Drosha. Sci Rep. 2013; 3:1942.
13. Allegra D, Bilan V, Garding A, Döhner H, Stilgenbauer S, Kuchenbauer F, Mertens D. Defective DROSHA processing contributes to downregulation of MiR-15/-16 in chronic lymphocytic leukemia. Leukemia. 2014;28(1):98.
14. Rupaimoole R, Slack FJ. MicroRNA therapeutics: towards a new era for the management of cancer and other diseases. Nat Rev Drug Discov. 2017;16(3):203–22. https://doi.org/10.1038/nrd.2016.246. Published online 17 Feb 2017.
15. Suzuki H, Maruyama R, Yamamoto E, Kai M. DNA methylation and microRNA dysregulation in cancer. Mol Oncol. 2012;6(6):567–78.
16. Fabbri M, Garzon R, Cimmino A, Liu Z, Zanesi N, Callegari E, Liu S, Alder H, Costinean S, Fernandez-Cymering C, Volinia S. MicroRNA-29 family reverts aberrant methylation in lung cancer by targeting DNA methyltransferases 3A and 3B. Proc Natl Acad Sci USA. 2007;104(40):15805–10.
17. Kim DH, Sætrom P, Snøve O, Rossi JJ. MicroRNA-directed transcriptional gene silencing in mammalian cells. Proc Natl Acad Sci USA. 2008;105(42):16230–5.
18. Place RF, Li LC, Pookot D, Noonan EJ, Dahiya R. MicroRNA-373 induces expression of genes with complementary promoter sequences. Proc Natl Acad Sci USA. 2008;105(5):1608–13.
19. Geary RS, Watanabe TA, Truong L, Freier S, Lesnik EA, Sioufi NB, Sasmor H, Manoharan M, Levin AA. Pharmacokinetic properties of 2′-O-(2-methoxyethyl)-modified oligonucleotide analogs in rats. J Pharmacol Exp Ther. 2001;296(3):890–7.
20. Li Q, Shao Y, Zhang X, Zheng T, Miao M, Qin L, Wang B, Ye G, Xiao B, Guo J. Plasma long noncoding RNA protected by exosomes as a potential stable biomarker for gastric cancer. Tumor Biol. 2015;36(3):2007–12.
21. Delangle R, De Foucher T, Larsen AK, Sabbah M, Azaïs H, Bendifallah S, Daraï E, Ballester M, Mehats C, Uzan C, Canlorbe G. The use of microRNAs in the management of endometrial cancer: a meta-analysis. Cancers. 2019;11(6):832.
22. Torres A, Torres K, Pesci A, Ceccaroni M, Paszkowski T, Cassandrini P, Zamboni G, Maciejewski R. Deregulation of miR-100, miR-99a and miR-199b in tissues and plasma coexists with increased expression of mTOR kinase in endometrioid endometrial carcinoma. BMC Cancer. 2012;12(1):369.
23. Boren T, Xiong Y, Hakam A, Wenham R, Apte S, Wei Z, Kamath S, Chen DT, Dressman H, Lancaster JM. MicroRNAs and their target messenger RNAs associated with endometrial carcinogenesis. Gynecol Oncol. 2008;110(2):206–15.
24. Wu W, Lin Z, Zhuang Z, Liang X. Expression profile of mammalian microRNAs in endometrioid adenocarcinoma. Eur J Cancer Prev. 2009;18(1):50–5.
25. Chung TK, Cheung TH, Huen NY, Wong KW, Lo KW, Yim SF, Siu NS, Wong YM, Tsang PT, Pang MW, Yu MY. Dysregulated microRNAs and their predicted targets associated with endometrioid endometrial adenocarcinoma in Hong Kong women. Int J Cancer. 2009;124(6):1358–65.
26. Mozos A, Catasús L, D'Angelo E, Serrano E, Espinosa I, Ferrer I, Pons C, Prat J. The FOXO1-miR27 tandem regulates myometrial invasion in endometrioid endometrial adenocarcinoma. Hum Pathol. 2014;45(5):942–51.
27. Dai Y, Xia W, Song T, Su X, Li J, Li S, Chen Y, Wang W, Ding H, Liu X, Li H. MicroRNA-200b is overexpressed in endometrial adenocarcinomas and enhances MMP2 activity by down-

regulating TIMP2 in human endometrial cancer cell line HEC-1A cells. Nucleic Acid Ther. 2013;23(1):29–34.
28. Hiroki E, Suzuki F, Akahira JI, Nagase S, Ito K, Sugawara JI, Miki Y, Suzuki T, Sasano H, Yaegashi N. MicroRNA-34b functions as a potential tumor suppressor in endometrial serous adenocarcinoma. Int J Cancer. 2012;131(4):e395–404.
29. Banno K, Kisu I, Yanokura M, Masuda K, Ueki A, Kobayashi Y, Susumu N, Aoki D. Epigenetics and genetics in endometrial cancer: new carcinogenic mechanisms and relationship with clinical practice. Epigenomics. 2012;4(2):147–62.
30. Liu P, Qi M, Ma C, Lao G, Liu Y, Liu Y, Liu Y. Let7a inhibits the growth of endometrial carcinoma cells by targeting Aurora-B. FEBS Lett. 2013;587(16):2523–9.
31. Chung TK, Lau TS, Cheung TH, Yim SF, Lo KW, Siu NS, Chan LK, Yu MY, Kwong J, Doran G, Barroilhet LM. Dysregulation of microRNA-204 mediates migration and invasion of endometrial cancer by regulating FOXC1. Int J Cancer. 2012;130(5):1036–45.
32. Zhou H, Xu X, Xun Q, Yu D, Ling J, Guo F, Yan Y, Shi J, Hu Y. microRNA-30c negatively regulates endometrial cancer cells by targeting metastasis-associated gene-1. Oncol Rep. 2012;27(3):807–12.
33. Kong X, Xu X, Yan Y, Guo F, Li J, Hu Y, Zhou H, Xun Q. Estrogen regulates the tumour suppressor MiRNA-30c and its target gene, MTA-1, in endometrial cancer. PLoS One. 2014;9(3):e90810.
34. Tan ZQ, Liu FX, Tang HL, Su Q. Expression and its clinical significance of hsa-miR-155 in serum of endometrial cancer. Zhonghua fu chan ke za zhi. 2010;45(10):772–4.
35. Yu S, Liu Y, Wang J, Guo Z, Zhang Q, Yu F, Zhang Y, Huang K, Li Y, Song E, Zheng XL. Circulating microRNA profiles as potential biomarkers for diagnosis of papillary thyroid carcinoma. J Clin Endocrinol Metab. 2012;97(6):2084–92.
36. Montagnana M, Benati M, Danese E, Giuidici S, Perfranceschi M. Aberrant microRNA expression in patients with endometrial cancer. Int J Gynecol Cancer. 2017;27:459–66.
37. Shang C, Lu YM, Meng LR. MicroRNA-125b down-regulation mediates endometrial cancer invasion by targeting ERBB2. Med Sci Monit. 2012;18(4):BR149.
38. Zhai H, Karaayvaz M, Dong P, Sakuragi N, Ju J. Prognostic significance of miR-194 in endometrial cancer. Biomarker Res. 2013;1(1):12.
39. Dong P, Kaneuchi M, Watari H, Hamada J, Sudo S, Ju J, Sakuragi N. MicroRNA-194 inhibits epithelial to mesenchymal transition of endometrial cancer cells by targeting oncogene BMI-1. Mol Cancer. 2011;10(1):99.
40. Lee LJ, Ratner E, Uduman M, Winter K, Boeke M, Greven KM, King S, Burke TW, Underhill K, Kim H, Boulware RJ, Yu H, Parkash V, Lu L, Gaffney D, Dicker AP, Weidhaas J. The KRAS-Variant and miRNA Expression in RTOG Endometrial Cancer Clinical Trials 9708 and 9905. PLoS One 2014;9(4):e94167.
41. Hiroki E, Akahira JI, Suzuki F, Nagase S, Ito K, Suzuki T, Sasano H, Yaegashi N. Changes in microRNA expression levels correlate with clinicopathological features and prognoses in endometrial serous adenocarcinomas. Cancer Sci. 2010;101(1):241–9.
42. Tsuruta T, Kozaki KI, Uesugi A, Furuta M, Hirasawa A, Imoto I, Susumu N, Aoki D, Inazawa J. miR-152 is a tumor suppressor microRNA that is silenced by DNA hypermethylation in endometrial cancer. Cancer Res. 2011;71(20):6450–62.
43. Jiang L, Meng W, Zeng J, Hu H, Lu L. MiR-34c oligonucleotide enhances chemosensitivity of Ishikawa cell to cisplatin by inducing apoptosis. Cell Biol Int. 2013;37(6):577–83.
44. Shen Y, Lu L, Xu J, Meng W, Qing Y, Liu Y, Zhang B, Hu H. Bortezomib induces apoptosis of endometrial cancer cells through micro RNA-17-5p by targeting p21. Cell Biol Int. 2013;37(10):1114–21.

Molecular Targeted Therapy in Endometrial Cancer: Basis and Therapeutics

12

Shruti Bhatia and Sunny Jandyal

Abbreviations

AKT	Protein kinase B
AMPK	Activated mitogen protein kinase
ARID1A	AT-rich interactive domain 1A
ARID5B	AT-rich interactive domain 5B
BER	Base excision repair
BRCA	Breast cancer type
CDK	Cyclin-dependent kinase
CHK-1	Checkpoint kinase 1
COX-2	Cyclooxygenase 2
CTNNB1	Catenin beta-1
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
ERα	Estrogen receptor α
ERBB	Erythroblastic leukemia viral oncogene
FBXW7	F-box and WD repeat domain containing protein 7
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
GOG	Gynecologic oncology
HER-2	Human epidermal growth factor 2
HR	Homologous recombination
IGF-1	Insulin growth factor-1
IGF-1R	Insulin growth factor-1 receptor
IgG	Immunoglobulin G

S. Bhatia (✉)
Department of Gyne Oncology, Action Cancer Hospital, Delhi, India

S. Jandyal
Department of Medical Oncology, Action Cancer Hospital, Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_12

JAK	Janus kinase
K-RAS	Kirsten rat sarcoma
MLH-1	MutL homolog 1
MMR	Mismatch repair
MSI	Microsatellite instability
MSH-2	MutS protein homolog 2
MSH-6	MutS homolog 6
MSS	Microsatellite stable
mTOR	Mammalian target of rapamycin
PARP	Poly-ADP ribose polymerase
PD	Programmed death
PDGF	Platelet-derived growth factor
PDGFR	Platelet-derived growth factor receptor
PDL	Programmed death ligand
PGE-2	Prostaglandin E2
PI3K	Phosphatidylinositol 3 kinase
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha
PIK3R1	Phosphatidylinositol 3-kinase regulatory subunit 1
PIP3	Phosphatidylinositol triphosphate
PMS-2	PMS1 Homolog 2, Mismatch Repair System Component
PPP2R1A	Protein phosphatase 2 scaffold subunit A alpha
PR	Progesterone receptors
PTEN	Phosphatase and tensin homolog
Raf	Rapidly accelerated fibrosarcoma
Ras	Rat sarcoma
RPL22	Ribosomal protein
SSB	Single strand breaks
STAT	Signal transducer and activator of transcription
TKI	Tyrosine kinase inhibitors
TNF-α	Tumor necrosis factor
TP53	Cellular tumor antigen p53
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

12.1 Introduction

Endometrial cancer (EC) is the third most common gynecologic cancer in India after cervical and ovarian cancer. In 2018, an estimated 13,328 new cases were diagnosed in India, and approximately 5000 deaths were attributed to this disease [1]. The increasing incidence in India and worldwide is thought to be related in part to the rise of obesity and diabetes. EC is going to become a more prominent healthcare concern in the near future.

Majority of women with EC are diagnosed at an early stage, which carries an excellent outcome. However, women with advanced stage and those with recurrent disease have extremely poor outcomes, with 5-year survival rates close to 20% [2].

The mainstay of treatment for EC is surgery (staging with hysterectomy, bilateral salpingo-oophorectomy, and with or without lymphadenectomy). Adjuvant radiotherapy is considered for a subset of high-risk cases. Radiation decreases local recurrence rates but does not affect relapse at distant sites or increase overall survival (OS). Adjuvant chemotherapy is given for advanced stages. The most active systemic agents are platinum compounds, taxanes, and anthracyclines, all of which produce a response rate of 20–30% [3]. However, response rates for metastatic and recurrent disease are lower, and there are no standard second-line therapies. Only one new drug, pembrolizumab has been approved in the last three decades for recurrent/advanced EC, and that too for a very small patient subset. There is an urgent need for new therapeutic approaches. As in many cancers, one such approach could be studying the tumor biology of this disease with targeting of specific molecular pathways.

Advances in understanding of molecular events leading to EC and molecular classification of EC have generated new avenues for targeting the disease. Common agents include drugs that affect apoptosis, signal transduction, epigenetic modification, drug resistance, cell cycle progression, hormone receptor activity, and angiogenesis. This is the basis of PORTEC-4a (Postoperative radiation therapy in endometrial carcinoma) trial which is comparing standard vaginal brachytherapy with different adjuvant treatments based on the integrated molecular profile [4]. The trial is ongoing and final results are awaited. Several other studies are exploring the role of immunotherapy in combination with paclitaxel and carboplatin, the role of metformin, and the role of PARP inhibitors. Many of these strategies appear promising in the treatment of recurrent or advanced disease.

In this chapter we will discuss the potential molecular targets and their therapeutic possibilities for EC.

12.1.1 Types of Endometrial Cancers

Historically, endometrial adenocarcinoma was divided into two histologic categories—type I and type II, as originally described by Bokhman in 1983 (Table 12.1) [5].

Table 12.1 Histologic classification of endometrial cancer

	Type I	Type II
Phenotype	Younger age Obese	Older age Nonobese
Pathogenesis	Estrogen dependent	Estrogen independent
Histology	Endometroid	Non-endometroid
Prognosis	Good	Poor
Molecular alterations	KRAS, PTEN, MSI, PI3K/AKT	p53, HER-2, Aneuploidy

- Type I: These tumors account for 70–80% of all new cases. They are usually seen in younger, obese, and premenopausal women. They have endometrioid histology, are low grade, and are estrogen driven. Patients with type I endometroid adenocarcinoma have high rates of K-RAS and PTEN loss or mutations, as well as MSI.
- Type II: This subtype comprises non-endometroid histology, high grade, estrogen-independent tumors, that usually have a poor outcome. These tumors are seen in women of older age group. They have high rates of p53 mutations, may overexpress HER-2, and show aneuploidy.

Although useful in many ways, there are limitations to this classification. Recently, The Cancer Genome Atlas (TCGA) project in 2013 reclassified EC based on genomic, transcriptomic, and proteomic differences studied in 373 primary EC surgical specimens (Table 12.2). The four subtypes described as per TCGA are: (1) polymerase epsilon catalytic subunit (POLE) ultramutated, (2) microsatellite instability (MSI)-hypermutated, (3) copy number low (CNL)-microsatellite stable, and (4) copy number high (CNH)-serous-like [6].

Table 12.2 TCGA genomic characterization of endometrial cancer

	POLE ultramutated	MSI-hypermutated	Copy number low	Copy number high
Histological features	Endometroid, broad front invasion, peri-tumor lymphocytes	Endometroid, lymphovascular invasion, lower uterine segment involvement	Endometroid, low grade, squamous differentiation, ER/PR	Serous, mixed histology, grade 3, high nuclear atypia
Clinical features	Lower BMI, early stage	Higher BMI, Lynch syndrome	Higher BMI	Lower BMI, advanced stage
Prognosis	Good	Intermediate	Variable	Poor
Suggested treatment options	Immune checkpoint inhibitors	Immune checkpoint inhibitors	Hormonal therapy, mTOR inhibitors	Small molecule activators of p53, PARP inhibitors
Mutation frequency per megabase (Mb)	>100/Mb	100-10/Mb	<10/Mb	<10/Mb
Microsatellite stability	Mixed	Instable	Stable	Stable
Frequent molecular alterations	POLE, PTEN, PIK3CA PIK3R1, FBXW7, ARID1A, KRAS, ARID5B	PTEN, RPL22, KRAS, PIK3CA, PIK3R1, ARID1A	PTEN, CTNNB, PIK3CA, PIK3R1, ARID1A	TP53, PPP2R1A, PIK3CA

1. POLE-ultramutated: This subgroup is characterized by very high somatic mutation rate, endometrioid histology, and is associated with good prognosis. It makes up only 1% of recurrent disease. The most commonly seen mutations in this subgroup are PTEN, PIK3CA, PIK3R1, FBXW7, ARID1A, KRAS, and ARID5B.
2. MSI-hypermutated: This subgroup is characterized by MSI due to dysfunctional mismatch repair genes, and mostly have an endometrioid histology. This subgroup comprises around 25% cases of recurrent disease. The most commonly seen mutations in this subgroup are PTEN, RPL22, KRAS, PIK3CA, PIK3R1, and ARID1A.
3. CNL-microsatellite stable: This subgroup is characterized by lower mutation rates, microsatellite stable, low-grade tumors, with endometrioid histology. The most common mutations in this subgroup are PTEN, CTNNB1, PIK3CA, PIK3R1, and ARID1A.
4. CNH-serous like: This subgroup is characterized by the lowest mutation rates, serous-like histology, chromosomal instability, and worse prognosis. The most common mutations seen in this subgroup are TP53, PPP2R1A, and PIK3CA.

12.2 Therapeutic Strategies

12.2.1 Obesity and Anti-inflammatory Agents

Obesity is an important risk factor for EC. It is also associated with an increased risk of recurrence and mortality from EC. An excess adipose tissue in obesity may increase the risk of cancer development by a number of mechanisms, like chronic inflammation, dysregulation of sex hormones, insulin resistance, altered immune response, and abnormal secretion of cytokines. Adipose tissue is an endocrine organ, producing the enzyme aromatase which leads to increased production of estrone from androstenedione. The increased estrogen levels lead to direct stimulation of endometrial cells by activating estrogen receptor alpha (ERα). Hyperinsulinemia seen in obesity decreases the levels of sex hormone-binding globulin (SHBG) by inhibiting its production in the liver. Lower levels of SHBG result in elevation of bioavailable estrogens, thus stimulating endometrial cells. Secondly, hyperinsulinemia leads to decreased levels of insulin like growth factor (IGF)-binding proteins, which results in elevated levels of free IGF-1. IGF-1 receptors are present in endometrial tissue and have been shown to stimulate endometrial cell proliferation. The binding of IGF-1 receptor ligand leads to autophosphorylation and subsequent activation of multiple downstream signaling pathways. Of these, the most important is PI3K/AKT/mTOR pathway (to be discussed in detail below). There is inactivation of AMPK pathway, which is commonly seen in obesity. This further leads to hyperactivity of mTOR and tumorigenesis in the endometrium (Fig. 12.1) [7, 8].

Adipose tissue also secretes adipokines like leptin, and pro-inflammatory cytokines like tumor necrosis factor alpha (TNF-α), and interleukins. These inflammatory agents cause hyperactivation of PI3K/AKT pathway and increased production

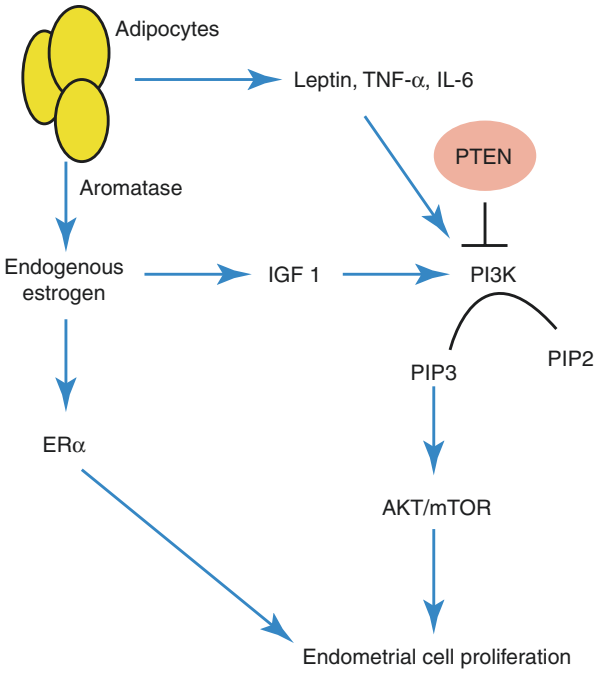


Fig. 12.1 Obesity and endometrial cancer. Adipose tissue produces pro-inflammatory adipokines leading to insulin resistance and stimulation of PI3K/AKT/mTOR pathway resulting in endometrial cell proliferation. Hyperestrogenism produced by peripheral conversion of androstenedione to estrogen by aromatase enzyme in adipocytes leads to direct stimulation of endometrial cells. *TNF* Tumor necrosis factor, *IL* interleukin, *PTEN* phosphatase and tensin homolog, *PI3K* phosphatidylinositol 3 kinase, *PIP2* phosphatidylinositol biphosphate, *PIP3* phosphatidylinositol triphosphate, *AKT* protein kinase B, *mTOR* mammalian target of rapamycin, *IGF* insulin growth factor, *ER* estrogen receptor

of COX-2 and PGE-2. Overexpression of COX-2 and PGE-2 has been linked to carcinogenesis, as they inhibit apoptosis, and promote angiogenesis [9]. In opposition to the pro-inflammatory adipokines, adiponectin reverses insulin resistance and acts as an anti-inflammatory agent. It inhibits tumor progression by inhibiting PI3K/AKT/mTOR signaling pathway [8]. Anti-inflammatory agents like aspirin and COX-2 inhibitors are therefore being investigated as possible therapeutic options in EC [10].

12.2.2 Hormonal Treatment

Hormonal therapy is not recommended routinely in the adjuvant setting, but it is still used for the management of recurrent and metastatic low-grade endometrioid EC. Megestrol acetate, a progestin that has been in use for over 40 years, was the first U.S. Food and Drug Administration (FDA) approved targeted therapy in

EC. However, the efficacy of megestrol acetate has been inconsistent, and according to a 2010 Cochrane review there has been no survival benefit for women receiving endocrine therapy for advanced EC [11]. The main predictors of response to hormonal agents are type I estrogen-dependent endometroid variety, well-differentiated histology, and expression of ER/PR receptors.

Various strategies have been tried to exploit the hormonal dependence of EC. Hormonal agents used for the treatment of EC have included systemic progestins (megestrol acetate, medroxyprogesterone acetate), levonorgestrel intrauterine device, selective estrogen receptor modulators (SERM) like tamoxifen, aromatase inhibitors (anastrozole, letrozole), and selective estrogen receptor downregulators (SERD) like fulvestrant. They can be used alone or in combination.

(A) *Single Agents*

1. Progestins: These agents counter the hyperestrogenism associated with EC. Single-agent progestins have yielded overall response rates between 20 and 25%. Studies have suggested that ERα or PR expressing cancers are more likely to respond, although the overall data are still inconsistent [12]. Oral medroxyprogesterone acetate 200 mg/day has shown favorable results in well-differentiated, PR-positive advanced or recurrent EC [13]. High-dose megestrol acetate in advanced and recurrent EC showed a clinical response of 24%, but the responses were short-lived [14]. The short duration of response was attributed to the downregulation of the PR. Levonorgestrel releasing intrauterine device has been used in women with early-stage and low-grade endometrioid EC who want to preserve fertility [15]. The results have been encouraging and it is now the preferred treatment in women desiring fertility with grade 1, endometrioid EC, with disease limited to the endometrium.
2. Aromatase inhibitors: In postmenopausal women, estrone produced by aromatase conversion of androstenedione is the main source of estrogen. Aromatase enzyme inhibitors—anastrazole and letrozole—have been used in EC, but with limited efficacy [16, 17]. They have shown some benefits in early-stage EC, but not in advanced or recurrent stage [18]. There is a need for newer generation aromatase inhibitors with fewer side effects and higher receptor specificity.
3. Fulvestrant: It is the only compound among SERDs approved by the FDA for use in the treatment of EC. Phase I/II trials have been performed, and have shown a good tolerability profile. It may be clinically efficacious due to its pure estrogen antagonist properties. However, the reported response rates (RR) have been low [19]. Further trials are ongoing to validate the dosing and also to study its use in combination with mTOR inhibitors [20].

(B) *Combination strategies*

1. Megestrol and tamoxifen: Tamoxifen increases the expression of progesterone receptors, thereby increasing the efficacy of megestrol acetate. This has been the basis of the GOG-153 study which evaluated the response of tamoxifen 20 mg twice daily every 3 weeks alternating with megestrol ace-

tate at 80 mg twice daily every 3 weeks. An RR of 27% was obtained with this strategy [21]. This combination also showed an increased durability of response, with more than half the responses lasting more than 20 months.

2. Hormonal agents and mTOR inhibitors: Hyperestrogenism leads to stimulation of PI3K/AKT/mTOR pathway (as explained above). Targeting this pathway has been proposed as a mechanism to overcome resistance to hormonal therapy. A phase II trial of everolimus (an mTOR inhibitor) and letrozole in patients of recurrent EC resulted in an objective RR of 32%, and median progression-free survival (PFS) of 3 months [22]. The limited response was due to incomplete blockade of mTOR complex by the mTOR inhibitors, and due to intra-pathway feedback loops. Another strategy to increase the efficacy of hormonal therapy efficacy would be to target multiple pathways. However, a phase II study of letrozole, everolimus, and metformin resulted in RR of only 29% [23]. Another study on the combination of temsirolimus (an mTOR inhibitor), megestrol, and tamoxifen, also reported an RR of only 14% and a high incidence of venous thromboembolism [24].
3. Hormonal agents and cyclin-dependent kinase (CDK) inhibitors: The combination of CDK4/6 inhibitors (to be discussed later) with hormonal therapy is a proven beneficial strategy in metastatic breast cancer. Elevated CDK4 expression has been seen in 34–77% of endometrioid EC [25]. Currently, studies are ongoing evaluating the role of palbociclib (CDK4/6 inhibitor) in combination with letrozole (NCT 02730429) and ribociclib (cyclin D1 and CDK4/6 inhibitor) in ER-positive advanced EC (NCT 02657928).

To summarize, hormonal therapy is recommended in recurrent or advanced stages of low-grade endometrioid EC, preferably in patients with small tumor volume or indolent growth rate. Medroxyprogesterone acetate, megestrol acetate, and levonorgestrel intrauterine device have also been recommended for hormonal treatment in women with EC desiring fertility (NCCN category IIA recommendations) [26].

12.2.3 Metformin

Metformin is an oral biguanide. It has recently gained importance as a potential anticancer agent in EC. There is epidemiological data suggesting that metformin use decreases the rate and risk of cancer deaths among diabetic patients [27, 28]. Studies have shown that metformin inhibits cellular proliferation and induces apoptosis, potentially by inhibiting the mTOR pathway. This is through the activation of AMPK and suppression of IGF-1/PI3K/AKT pathway. An indirect mechanism for metformin effect may be the inhibition of liver gluconeogenesis resulting in a decrease in insulin levels and reduced hyperglycemia. In vitro studies have also shown inhibition of EC cells treated with metformin [29, 30].

Various studies have shown improved OS and recurrence-free survival with metformin in diabetic EC patients, in combination with chemotherapy [31, 32]. Although some authors did not find any effect of metformin exposure on survival

parameters [33], a 2017 meta-analysis supports a higher OS rate in metformin users with EC compared to non-metformin users and nondiabetic patients [34]. Another meta-analysis of 28 studies reported that metformin use was associated with decreased all-cause mortality in patients with concurrent diabetes for several cancer types, including EC [35].

Currently, metformin is being evaluated in recurrent/advanced EC in combination with standard cytotoxic chemotherapy (NCT 02065687) and with hormonal and mTOR agents (NCT 01797523). Overall, studies have shown promise for metformin as an adjunctive treatment for EC. However, further studies are needed to define its exact therapeutic role in EC.

12.2.4 PTEN/PI3K/AKT/mTOR Pathway Inhibitors

The phosphatidylinositol 3 kinase (PI3K) pathway is the most frequently altered pathway in human tumors, and EC has a very high incidence of PI3K pathway alterations. Approximately 40% of serous EC and over 70% of endometrioid EC have PI3K pathway aberration [36]. PTEN located on chromosome 10 encodes a phospholipid called phosphatase and tensin homolog and acts as a tumor suppressor gene by inhibiting the PI3K signaling pathway. PTEN expression in endometrium is regulated by estrogen and progesterone levels in blood. PTEN inactivation has been implicated in the development of EC. Inactivation of PTEN usually occurs as a result of deletional or mutational events, and less by promoter methylation. When PTEN is suppressed, there is upregulation of PI3K and mTOR activity which leads to increased tumor cell proliferation, migration, and invasion.

PI3K signaling pathway is initiated through multiple receptor tyrosine kinases, including EGFR, HER-2, IGF-1R, VEGFR, PDGF, and Src family kinases. PI3K in turn activates protein kinase B, also called AKT. Through a series of downstream effectors AKT leads to activation of mTOR. mTOR is a serine-threonine protein kinase that ultimately triggers cell proliferation through several downstream moieties. It forms the core of two regulatory complexes—mTORc1 and mTORc2. As will be discussed later, everolimus and the newer mTOR inhibitors mainly target the mTORc1. PI3K inhibition potentially targets multiple aspects of tumor biology, including angiogenesis, inflammation, epithelial to mesenchymal transition, and metastasis. Its integral role in immune modulation may make PI3K inhibitors ideal partners for immune checkpoint inhibitors [37–39].

Rapamycin is an antibiotic derived from *Streptomyces hygroscopicus* and is known to inhibit the proliferation of endometrial cancer cells in vitro. The rapamycin analogs (rapalogs) used in clinical trials include everolimus, temsirolimus, deforolimus, and ridaforolimus [40–43]. These agents inhibit cytokine and growth-factor dependent cell proliferation through the inhibition of mTORc1. Increases in mTORc2 may be a means of therapeutic resistance to these agents. Thus efforts are underway to develop more potent dual mTORc1 and mTORc2 inhibitors.

Clinical experience with the rapamycin analogs has shown modest results. In a study of 54 patients, temsirolimus showed a response rate of 14% in

chemotherapy-naïve patients [44]. NCCN panel has recommended (level IIa evidence) temsirolimus for the treatment of EC patients who have progressed on previous chemotherapy [26].

Targeting the PI3K/AKT/mTOR pathway alone or in combination remains an active area of research in EC. A study is going on to examine the role of the PI3K inhibitor, copanlisib, in patients with PI3KCA hot spot mutations in their EC (NCT02728258). Some of the studies combining hormonal agents with inhibitors of mTOR pathway have been mentioned in the section on hormonal agents above.

12.2.5 PARP Inhibitors

Poly-ADP ribose polymerases (PARPs) are a family of nuclear enzymes that regulate the repair of DNA single-strand breaks (SSBs) through the base excision repair (BER) pathway. Upon DNA damage, PARP cleaves nicotine adenine dinucleotide (NAD) to generate poly-ADP-ribose (PAR) polymers, which are then added on to DNA, histones, and DNA repair proteins. These processes lead to the recruitment of the cellular repair machinery which facilitates the BER process.

BRCA-1 and BRCA-2 genes encode proteins involved in the homologous recombination (HR) repair of double-stranded breaks. Tumors with mutations in BRCA-1 and BRCA-2 are dependent on the BER rescue pathway for DNA damage repair. Inhibition of PARP leads to the accumulation of DNA double-strand breaks in HR-deficient, BRCA-1/2 mutated tumor cells. This induces cellular apoptosis. Hence, PARP inhibitors may be effective in tumor subtypes with BRCA mutations, and this mechanism of targeted therapy with PARP inhibitors in BRCA mutant tumors has been named "synthetic lethality." PARP inhibitors like olaparib, rucaparib, and niraparib have been approved for clinical use in BRCA-1/2 mutated ovarian cancers. HR deficiency due to BRCA-1/2 mutation occurs in many EC, especially in non-endometroid, TP53-mutant tumors.

As described above, PTEN acts as a tumor suppressor gene by inhibiting the PI3K/AKT/mTOR pathway. PTEN also plays a tumor-suppressive role in the nucleus by maintaining genome integrity. Loss of PTEN impairs CHK1 function, leading to the accumulation of DNA double-strand breaks and genomic instability. PTEN also regulates the expression of RAD51, a key protein in HR repair of DNA double-strand breaks. PTEN deficiency may also be predictive of sensitivity to PARP inhibitors like BRCA-1/2 mutation [45, 46]. However, there are conflicting results regarding the synthetic lethal targeting of PTEN-deficient EC cells with PARP inhibitors.

Olaparib has shown good results in a single study [47]. However, another study has shown that some PTEN-mutated EC cell lines were not sensitive to this agent [48]. The reasons for the reported difference in responses are not yet clear. Niraparib is being studied in patients with recurrent/advanced EC (NCT 03016338). PARP inhibitors in combination with cytotoxic agents have also shown promising results in the treatment of advanced/recurrent EC [49]. Studies are ongoing to look for newer PARP inhibitor drugs (BMN-673) which may be more efficacious [50]. Currently, PARP inhibitors are not a part of the routine treatment of EC.

12.2.6 Antiangiogenic Therapy

Angiogenesis is a crucial process involved in the growth and progression of solid tumors. Vascular endothelial growth factor (VEGF) generated from the cancer cells induces new blood vessel formation by stimulating endothelial cell proliferation and migration. The activated endothelial cells release matrix metalloproteinases to break down the surrounding extracellular matrix to promote new vessel formation [51, 52].

VEGF family includes three transmembrane receptors—VEGF1, VEGF2, and VEGF3. Each of these three receptors serve distinct biological functions. Binding of the VEGF ligand to its receptor activates the downstream PI3K/AKT/mTOR pathway. VEGF has been correlated with high-grade histology, lymphovascular space invasion, deep myometrial invasion, and lymph node metastases in EC [53].

Bevacizumab has been the most studied antiangiogenic drug. It is a recombinant humanized IgG2 monoclonal antibody that binds to circulating VEGF, and prevents it from binding to its receptors. The drug also normalizes tumor vessels that are structurally and functionally abnormal. This may enhance the effect of other chemotherapeutic drugs also. Adverse events are hypertension, proteinuria, and major gastrointestinal toxicities like perforation and fistula formation. Bevacizumab has been approved for ovarian cancer patients in both primary and recurrent settings. It has also shown favorable response in cervical cancer. A GOG phase II trial of bevacizumab as monotherapy in recurrent/persistent EC in 2011 found it to be well tolerated and showed PFS of 6 months [54].

A limitation with using a monoclonal antibody is that they cannot directly target the downstream intracellular pathways, which are usually redundant with multiple converging stimuli. To target other elements in the VEGF signaling cascade, bevacizumab has been combined with other small molecules, including TKI. Phase II studies have shown improved PFS with bevacizumab in combination with mTOR inhibitors [55]. Other retrospective studies have shown high PFS and OS in patients who received bevacizumab, paclitaxel, and carboplatin regimen as first-line therapy in advanced and recurrent EC [56–58]. Although no antiangiogenic drug has been approved by the FDA for therapy of EC, the NCCN panel considers bevacizumab as an appropriate single-agent therapy for patients who have progressed on previous cytotoxic chemotherapy [26]. Recently, the addition of bevacizumab to radiotherapy has been found to be beneficial in improving local disease control [59, 60].

12.2.7 CDK Inhibitors

Cyclins and cyclin-dependent kinases (CDK) are the main regulators of progression through the cell cycle. CDKs are serine/threonine protein kinases that phosphorylate nuclear target proteins involved in the cell cycle. Different types of cyclins are specific for each phase of the cell cycle. They are synthesized during one cycle phase and subsequently degraded during the succeeding phase. A cyclin forms a complex with its corresponding CDK, which leads to the activation of CDK. CDK 4/6 promote the G1/S phase transition by phosphorylating and inactivating the

retinoblastoma protein (Rb), and lead to cell cycle progression. Cyclin D1 is the upstream activator of CDK 4/6. Cyclin D1 amplification is observed in more than one-third of endometrioid ECs [61].

CDK inhibitors can arrest the cell cycle, and CDK4/6 targeted therapy has become an important strategy in endocrine-resistant breast cancer. Currently, phase II trials are ongoing to evaluate the role of CDK 4/6 inhibitor palbociclib, and cyclin D1 and CDK 4/6 inhibitor ribociclib in ER-positive advanced or recurrent EC (NCT 02730429 and NCT 02657928). Ribociclib is currently under phase II trial for use in advanced/recurrent EC, in combination with letrozole and the mTOR inhibitor temsirolimus (NCT 03008408).

12.2.8 Tyrosine Kinase Inhibitors

Tyrosine kinase receptors (TKR) are a family of transmembrane glycoproteins that are usually activated by a variety of growth factors. The important TKRs involved in EC include HER-2, EGFR, FGFR2, and VEGFR. Kinases play a crucial role in major cell functions like cell cycle progression, signal transduction, and transcription. As a result, TKRs have become an important target for cancer therapy. TKIs interfere with intracellular signaling pathways by preventing kinases from catalyzing the transfer of the γ phosphate group from adenosine triphosphate to target proteins. Multiple oral TKIs have become available for a variety of tumors. Their role in EC is also under evaluation.

Geftinib, erlotinib, lapatinib, and imatinib are small molecule inhibitors of EGFR-tyrosine kinase pathway. A phase II trial of erlotinib in recurrent or metastatic EC showed a response rate of 12.5% [62]. Cediranib, a TKI targeting VEGF, PDGF, and FGF receptors has been studied in recurrent or persistent EC. The phase II trial of this study showed a median OS of 12.5 months with no severe toxicities [63].

12.2.9 ERBB-2/HER-2 Inhibitors

HER-2 receptor belongs to the EGFR family. EGFR family consists of four distinct cell surface receptors—ERBB-1, ERBB-2/HER-2, ERBB-3, and ERBB-4. Upon ligand binding, these transmembrane proteins form homo- or heterodimers that lead to activation of their intracellular tyrosine kinase domain. Downstream signaling pathways of the HER-2 receptors include the Ras/Raf/AMPK, PI3K/AKT/mTOR, and JAK/Stat pathways [64]. These three pathways govern key cellular functions such as cell proliferation, survival, and apoptosis, and also cell migration and metastases. HER-2 is amplified in 21–47% of serous ECs, found in the TCGA CNH subgroup, and in 3–21% of endometrioid ECs [65, 66].

Trastuzumab is a humanized monoclonal antibody that binds to the extracellular domain of the HER-2 receptor, leading to inhibition of downstream signaling. The clinical efficacy of trastuzumab has been reported in several case reports, in patients

with recurrent or advanced EC [67, 68]. However, a phase II study evaluating the role of trastuzumab for HER-2 expressing recurrent/advanced EC found no objective response [69]. Similarly, a phase II study of lapatinib (HER-2 inhibitor) in unselected patients with recurrent or persistent EC observed limited clinical activity [70].

A recent randomized phase II study examined the effect of adding trastuzumab to carboplatin/paclitaxel for patients with advanced HER-2 positive serous EC. They found significant improvement in PFS without an increase in overall toxicity [71]. However, the patient number in this study was small (n= 63) and further phase III studies with higher patient population are needed, which may be difficult considering the low incidence of serous EC. Currently, phase II studies are undergoing to evaluate the role of afatinib (a pan ERBB inhibitor) and ado-trastuzumab emtansine (NCT 02491099 and NCT 02675829) in EC.

In summary, the role of HER-2 and ERBB targeted therapy in combination with cytotoxic drugs in EC is under evaluation, and future studies will define its role in recurrent and metastatic EC.

12.2.10 Immunotherapy and Microsatellite Instability

T cells are stimulated to elicit response to neoantigens through binding of T cell receptors (TCR) to major histocompatibility antigens (MHC) on the surface of antigen presenting cells (APC). Binding of CD28 on T cells and B7 on APC serves a co-stimulatory function. To modulate the immune response, T cells express programmed death 1 (PD-1), and cytotoxic T-lymphocyte (CTLA-4) antigens. PD-1 has two potential ligands on APCs, namely PD-L1 and PD-L2, while CTLA-4 binds to the B7 antigen on APC. These interactions promote T cell anergy.

Tumors may evade immune surveillance by various mechanisms like loss or alteration of specific antigens, promotion of an immune tolerant microenvironment by manipulation of cytokines, or by upregulation of immune checkpoint molecules such as PD-L1. Upregulation of PD-1/PD-L1 signaling enables tumors to “turn off” T cells and evade immune recognition [72].

The PD-1/PD-L1 complex is expressed on tumor-infiltrating immune cells of 60–80% of primary ECs and in 100% of metastatic EC [73]. The high mutation load in the POLE-mutated and MSI-H subgroups is also correlated with PD-1 and PD-L1 expression. These subgroups of EC patients may be appropriate candidates for immune checkpoint inhibitor therapy [74].

Immune checkpoint inhibitors include CTLA-4 inhibitors, PD-1 inhibitors, and PD-L1 inhibitors (Fig. 12.2). Pembrolizumab is a monoclonal antibody to PD-1, and promotes tumor cell apoptosis by binding to T cell PD-1 receptors. It has been shown to be effective in many solid tumors, especially those with MSI (described later). In the preliminary results from KEYNOTE-028 study, there was an objective RR of 13% in 24 patients with advanced PD-L1 positive EC who were treated with pembrolizumab. The drug demonstrated a favorable safety profile and durable antitumor activity in treatment-experienced patients with advanced disease [75].

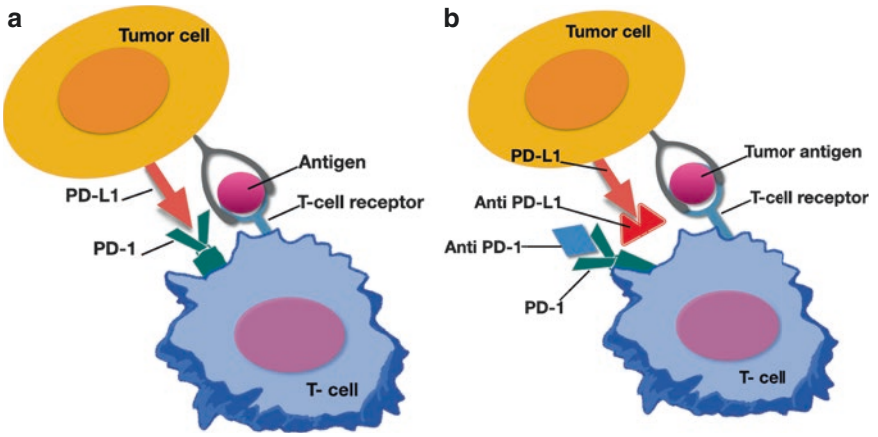


Fig. 12.2 (**a**) PD-L1/PD-1 binding inhibits T cell killing of tumor cells. (**b**) Blocking of PD-1 or PD-L1 enables T cell killing of tumor cells. *PD-1* programmed death 1, *PD-L1* programmed death ligand-1

Avelumab, a monoclonal antibody to PD-L1 is being studied in a phase II trial along with carboplatin and paclitaxel in recurrent/advanced EC (NCT03503786).

Microsatellites are noncoding sections of the DNA that consist of repeats of short sequences of nucleotides. Because of their repetitive nature, microsatellites have a tendency to develop errors during DNA replication. The mismatch repair genes are responsible for repairing these errors during DNA replication [76]. Tumors with a defect in DNA mismatch repair (MMR) mechanism show MSI. MMR abnormalities are usually due to a lack of MLH-1, MSH-2, MSH-6, and PMS-2 protein(s), which are essential for the process of repairing mismatch errors during DNA replication. MSI can be due to germline mutations involving the MMR genes (as in Lynch syndrome) or epigenetic defects [77, 78]. Epigenetic defects are due to MLH-1 promoter hypermethylation with consequent epigenetic silencing.

Lynch syndrome is an autosomal dominant disorder characterized by germline mutations in one of the DNA MMR genes and can be diagnosed by direct gene sequencing as directed by the tumor immunohistochemistry results. Lynch syndrome accounts for approximately 5% of EC cases. The lifetime risk of developing EC with Lynch syndrome varies with age and mutation of the specific MMR gene. Patients with MSH-6 mutations are at a higher risk (64–71% lifetime risk) for developing EC than those with MSH-2 or MLH-1 mutations (40–50% lifetime risk). MSI is not seen exclusively in Lynch syndrome. 15–25% of sporadic EC are MSI high (MSI-H), because of promoter-hypermethylation of MLH-1 gene as an epigenetic event [79, 80].

According to the TCGA, MSI is present in 30–40% of endometroid EC. EC with MSI has a propensity for lower uterine segment involvement, intratumoral heterogeneity, and intense peritumoral lymphocytic infiltration [81].

MSI status may be used to guide therapy in recurrent and metastatic EC. The incidence of somatic mutations is higher in tumors with MSI, and these tumors express significantly more neoantigens in comparison with microsatellite stable (MSS) EC [82, 83]. This high rate of somatic mutations as well as neoantigens makes MSI-H tumors an attractive target for immune-based therapies. MSI-H status may be a marker for response to anti-PD-1/PD-L1 antibodies [84, 85]. Recently, based on data from five single-arm, multicenter clinical trials including 149 patients, pembrolizumab has been granted accelerated approval by the FDA for tissue or site-agnostic use in unresectable or metastatic MSI-H solid tumors, including EC [86, 87]. It is recommended that recurrent EC cases should be tested for MSI status or defective MMR, if not done previously [88].

One recent multicenter study has reported a significant beneficial effect of pembrolizumab in combination with lenvatinib (a multi-kinase inhibitor of VEGFR 1−3, FGFR 1−4, PDGFR α, RET, and KIT) in 54 patients with previously treated, metastatic EC. An objective RR of 50% was found at 24 weeks. The patients enrolled in this study were not preselected based on MSI or PD-L1 status, and included 3 MSI-H, 43 MSI-low, and eight unknown MSI status patients. These encouraging results led FDA to grant "breakthrough therapy" designation for lenvatinib and pembrolizumab combination for the treatment of patients with advanced/metastatic non-MSI-H/proficient MMR EC who have progressed following at least one prior systemic therapy. A randomized, international, two-arm phase III study of pembrolizumab and lenvatinib combination in recurrent EC is underway [89, 90].

Other studies are evaluating the combination of immunotherapy with cytotoxic chemotherapy in EC. There is an ongoing phase II trial examining pembrolizumab plus carboplatin/paclitaxel in advanced or recurrent EC (NCT02549209). Thus, while single-agent immune checkpoint blockade has been successful in a subset of MSI-H and POLE EC patients, combination strategies will be necessary to overcome resistance to immunotherapy in the majority.

12.3 Conclusion

EC has a favorable prognosis in stages I and II. However, the outcome is poor in advanced/metastatic/recurrent disease. The optimal adjuvant treatment for these high-risk cases is largely unsettled. Platinum-based chemotherapy is being used currently in clinical practice, but the results are not very encouraging. The recent genomic characterization of EC has provided new insights and new potential opportunities. There is a need to integrate this molecular and histologic tumor stratification into the management strategy for EC. The paradigm of cancer treatment is moving from "one-size-fits-all" strategy to personalized therapy. Targeted therapies like antiangiogenic agents, TKIs, PARP inhibitors, and immunotherapy agents have shown promise in the treatment of EC. Increasing knowledge in cancer biology will allow the development of new treatments tailored to a particular signaling pathway, while minimizing the side effects.

12.4 Key Points

1. Endometrial cancer (EC) was initially divided into two types based on histology: type-I, endometroid variety, and type-II, non-endometroid variety. Based on molecular profiling, EC is now divided into four varieties: POLE ultramutated, MSI-hypermutated, copy number low, and copy number high.
2. Hormonal therapy is recommended in recurrent or advanced stages of low-grade endometrioid EC, preferably in patients with small tumor volume or indolent growth rate. Medroxyprogesterone acetate, megestrol acetate, and levonorgestrel intrauterine device have also been recommended as hormonal treatment in women with EC desiring fertility.
3. Metformin—an oral biguanide, is an effective drug for the management of diabetes which is a major risk factor for EC. It has also shown good results as an adjunctive drug for the management of EC, alone and in combination with standard chemotherapy. However, it is not yet an established adjuvant treatment of EC.
4. The PI3K/AKT/mTOR pathway is an important pathway for EC. Drugs targeting this pathway alone, or in combination are an active area of research in the treatment of EC.
5. PARP inhibitors—olaparib and niraparib have shown good results in the treatment of recurrent/advanced EC. However, they are not a part of routine treatment currently.
6. Bevacizumab, an antiangiogenic drug is recommended for use in recurrent EC cases who have progressed on previous cytotoxic chemotherapy.
7. CDK inhibitors like palbociclib, and ribociclib, and TKIs like gefitinib, erlotinib, lapatinib, and cediranib, and the HER-2 receptor inhibitor trastuzumab are currently under trial for use in advanced/recurrent EC.
8. Pembrolizumab, an immune checkpoint blocker, has been found to be successful in MSI-H and POLE subset of EC patients. It is recommended for use in metastatic EC cases with MSI-H status.
9. MSI testing is becoming increasingly important in many cancers including EC. MSI can be sporadic or associated with Lynch syndrome. NCCN guidelines recommend universal testing of all EC cases for MSI status.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
2. Creasman WT, Odicino F, Maisonneuve P, Quinn MA, Beller U, Benedet JL, et al. Carcinoma of the corpus uteri. FIGO 26th annual report on the results of treatment in gynecological cancer. Int J Gynaecol Obstet. 2006;95(Suppl 1):S105–43.
3. Mountzios G, Pectasides D, Bournakis E, Pectasides E, Bozas G, Dimopoulos MA, et al. Developments in the systemic treatment of endometrial cancer. Crit Rev Oncol Hematol. 2011;79(3):278–92.

4. Wortman BG, Bosse T, Nout RA, Lutgens LCHW, van der Steen-Banasik EM, Westerveld H, et al. PORTEC Study Group. Molecular-integrated risk profile to determine adjuvant radiotherapy in endometrial cancer: evaluation of the pilot phase of the PORTEC-4a trial. Gynecol Oncol. 2018;151(1):69–75.
5. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10–7.
6. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497(7447):67–73.
7. Akhmedkhanov A, Zeleniuch-Jacquotte A, Toniolo P. Role of exogenous and endogenous hormones in endometrial cancer: review of the evidence and research perspectives. Ann N Y Acad Sci. 2001;943:296–315.
8. Schmandt RE, Iglesias DA, Co NN, Lu KH. Understanding obesity and endometrial cancer risk: opportunities for prevention. Am J Obstet Gynecol. 2011;205(6):518–25.
9. Jabbour HN, Milne SA, Williams AR, Anderson RA, Boddy SC. Expression of COX-2 and PGE synthase and synthesis of PGE(2)in endometrial adenocarcinoma: a possible autocrine/paracrine regulation of neoplastic cell function via EP2/EP4 receptors. Br J Cancer. 2001;85(7):1023–31.
10. Wang D, Dubois RN. Eicosanoids and cancer. Nat Rev Cancer. 2010;10(3):181–93.
11. Kokka F, Brockbank E, Oram D, Gallagher C, Bryant A. Hormonal therapy in advanced or recurrent endometrial cancer. Cochrane Database Syst Rev. 2010;8(12):CD007926.
12. Markman M. Hormonal therapy of endometrial cancer. Eur J Cancer. 2005;41(5):673–5.
13. Thigpen JT, Brady MF, Alvarez RD, Adelson MD, Homesley HD, Manetta A, 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(6):1736–44.
14. Lentz SS, Brady MF, Major FJ, Reid GC, Soper JT. High-dose megestrol acetate in advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. J Clin Oncol. 1996;14(2):357–61.
15. Laurelli G, Falcone F, Gallo MS, Scala F, Losito S, Granata V, et al. Long-term oncologic and reproductive outcomes in young women with early endometrial cancer conservatively treated: a prospective study and literature update. Int J Gynecol Cancer. 2016;26(9):1650–7.
16. Ma BB, Oza A, Eisenhauer E, Stanimir G, Carey M, Chapman W, et al. 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.
17. 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.
18. Gao C, Wang Y, Tian W, Zhu Y, Xue F. The therapeutic significance of aromatase inhibitors in endometrial carcinoma. Gynecol Oncol. 2014;134(1):190–5.
19. Emons G, Günthert A, Thiel FC, Camara O, Strauss HG, Breitbach GP, et al. Phase II study of fulvestrant 250 mg/month in patients with recurrent or metastatic endometrial cancer: a study of the Arbeitsgemeinschaft Gynäkologische Onkologie. Gynecol Oncol. 2013;129(3):495–9.
20. Bogliolo S, Cassani C, Dominoni M, Orlandini A, Ferrero S, Iacobone AD, et al. The role of fulvestrant in endometrial cancer. Expert Opin Drug Metab Toxicol. 2017;13(5):537–44.
21. Fiorica JV, Brunetto VL, Hanjani P, Lentz SS, Mannel R, Andersen W; Gynecologic Oncology Group Study. Phase II trial of alternating courses of megestrol acetate and tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92(1):10–4.
22. Slomovitz BM, Jiang Y, Yates MS, Soliman PT, Johnston T, Nowakowski M, Levenback C, et al. Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma. J Clin Oncol. 2015;33(8):930–6.
23. Soliman PT, Westin SN, Iglesias DA, et al. Phase II study of everolimus and letrozole in women with advanced/recurrent endometrial cancer. J Clin Oncol. 2016; 34(15-suppl):5506.

24. Fleming GF, Filiaci VL, Marzullo B, Zaino RJ, Davidson SA, Pearl M, et al. Temsirolimus with or without megestrol acetate and tamoxifen for endometrial cancer: a gynecologic oncology group study. Gynecol Oncol. 2014;132(3):585–92.
25. Shih HC, Shiozawa T, Kato K, Imai T, Miyamoto T, Uchikawa J, et al. Immunohistochemical expression of cyclins, cyclin-dependent kinases, tumor-suppressor gene products, Ki-67, and sex steroid receptors in endometrial carcinoma: positive staining for cyclin A as a poor prognostic indicator. Hum Pathol. 2003;34(5):471–8.
26. NCCN guidelines. Version 3.2019.
27. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ. 2005;330(7503):1304–5.
28. Libby G, Donnelly LA, Donnan PT, Alessi DR, Morris AD, Evans JM. New users of metformin are at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care. 2009;32(9):1620–5.
29. Cantrell LA, Zhou C, Mendivil A, Malloy KM, Gehrig PA, Bae-Jump VL. Metformin is a potent inhibitor of endometrial cancer cell proliferation—implications for a novel treatment strategy. Gynecol Oncol. 2010;116(1):92–8.
30. Zhao Y, Sun H, Feng M, Zhao J, Zhao X, Wan Q, et al. Metformin is associated with reduced cell proliferation in human endometrial cancer by inhibiting PI3K/AKT/mTOR signaling. Gynecol Endocrinol. 2018; 34(5):428–32.
31. Ko EM, Walter P, Jackson A, Clark L, Franasiak J, Bolac C, et al. Metformin is associated with improved survival in endometrial cancer. Gynecol Oncol. 2014;132(2):438–42.
32. Ezewuiro O, Grushko TA, Kocherginsky M, Habis M, Hurteau JA, Mills KA, et al. Association of metformin use with outcomes in advanced endometrial cancer treated with chemotherapy. PLoS One. 2016;11(1):e0147145.
33. Lemańska A, Zaborowski M, Spaczyński M, Nowak-Markwitz E. Do endometrial cancer patients benefit from metformin intake? Ginekol Pol. 2015;86(6):419–23.
34. Meireles CG, Pereira SA, Valadares LP, Rêgo DF, Simeoni LA, Guerra ENS, et al. A. Effects of metformin on endometrial cancer: systematic review and meta-analysis. Gynecol Oncol. 2017;147(1):167–80.
35. Zhang ZJ, Li S. The prognostic value of metformin for cancer patients with concurrent diabetes: a systematic review and meta-analysis. Diabetes Obes Metab. 2014;16(8): 707–10.
36. Hayes MP, Wang H, Espinal-Witter R, Douglas W, Solomon GJ. Baker SJ, et al PIK3CA and PTEN mutations in uterine endometrioid carcinoma and complex atypical hyperplasia. Clin Cancer Res. 2006;12(20 Pt 1):5932–5.
37. Hecht JL, Mutter GL. Molecular and pathologic aspects of endometrial carcinogenesis. J Clin Oncol. 2006;24(29):4783–91.
38. Maxwell GL, Risinger JI, Gumbs C, Shaw H, Bentley RC, Barrett JC, et al. Mutation of the PTEN tumor suppressor gene in endometrial hyperplasias. Cancer Res. 1998;58(12): 2500–3.
39. Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, Weng LP, Eng C. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst. 2000;92(11):924–30.
40. Abraham RT. Mammalian target of rapamycin: immunosuppressive drugs uncover a novel pathway of cytokine receptor signaling. Curr Opin Immunol. 1998;10(3):330–6.
41. Colombo N, McMeekin DS, Schwartz PE, Sessa C, Gehrig PA, Holloway R, et al. Ridaforolimus as a single agent in advanced endometrial cancer: results of a single-arm, phase 2 trial. Br J Cancer. 2013;108(5):1021–6.
42. Oza AM, Pignata S, Poveda A, McCormack M, Clamp A, Schwartz B, et al. Randomized phase II Trial of ridaforolimus in advanced endometrial carcinoma. J Clin Oncol. 2015;33(31):3576–82.
43. Ray-Coquard I, Favier L, Weber B, Roemer-Becuwe C, Bougnoux P, Fabbro M, et al. Everolimus as second- or third-line treatment of advanced endometrial cancer: ENDORAD, a phase II trial of GINECO. Br J Cancer. 2013;108(9):1771–7.

44. Oza AM, Elit L, Tsao MS, Kamel-Reid S, Biagi J, Provencher DM, et al. Phase II study of temsirolimus in women with recurrent or metastatic endometrial cancer: a trial of the NCIC Clinical Trials Group. J Clin Oncol. 2011;29(24):3278–85.
45. Dedes KJ, Wetterskog D, Mendes-Pereira AM, Natrajan R, Lambros MB, Geyer FC et al. PTEN deficiency in endometrioid endometrial adenocarcinomas predicts sensitivity to PARP inhibitors. Sci Transl Med. 2010;2(53):53ra75.
46. Koppensteiner R, Samartzis EP, Noske A, von Teichman A, Dedes I, Gwerder M, et al. Effect of MRE11 loss on PARP-inhibitor sensitivity in endometrial cancer in vitro. PLoS One. 2014;9(6):e100041.
47. Forster MD, Dedes KJ, Sandhu S, Frentzas S, Kristeleit R, Ashworth A, et al. Treatment with olaparib in a patient with PTEN-deficient endometrioid endometrial cancer. Nat Rev Clin Oncol. 2011;8(5):302–6.
48. Dillon LM, Miller TW. Therapeutic targeting of cancers with loss of PTEN function. Curr Drug Targets. 2014;15(1):65–79.
49. Dinkic C, Jahn F, Zygmunt M, Schuetz F, Rom J, Sohn C, et al. PARP inhibition sensitizes endometrial cancer cells to paclitaxel-induced apoptosis. Oncol Lett. 2017;13(4):2847–51.
50. Philip CA, Laskov I, Beauchamp MC, Marques M, Amin O, Bitharas J, et al. Inhibition of PI3K-AKT-mTOR pathway sensitizes endometrial cancer cell lines to PARP inhibitors. BMC Cancer. 2017;17(1):638.
51. Mazurek A, Telego M, Pierzyński P, Lapuć G, Nikliñska W, Juczewska M, et al. Angiogenesis in endometrial cancer. Neoplasma. 1998;45(6):360–4.
52. Ellis LM, Hicklin DJ. VEGF-targeted therapy: mechanisms of anti-tumour activity. Nat Rev Cancer. 2008;8(8):579–91.
53. Lee CN, Cheng WF, Chen CA, Chu JS, Hsieh CY, Hsieh FJ. Angiogenesis of endometrial carcinomas assessed by measurement of intratumoral blood flow, microvessel density, and vascular endothelial growth factor levels. Obstet Gynecol. 2000;96(4):615–21.
54. Aghajanian C, Sill MW, Darcy KM, Greer B, McMeekin DS, Rose PG, et al. Phase II trial of bevacizumab in recurrent or persistent endometrial cancer: a Gynecologic Oncology Group study. J Clin Oncol. 2011;29(16):2259–65.
55. Alvarez EA, Brady WE, Walker JL, Rotmensch J, Zhou XC, Kendrick JE, 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(1):22–7.
56. Simpkins F, Drake R, Escobar PF, Nutter B, Rasool N, Rose PG. A phase II trial of paclitaxel, carboplatin, and bevacizumab in advanced and recurrent endometrial carcinoma (EMCA). Gynecol Oncol. 2015;136(2):240–5.
57. Rose PG, Ali S, Moslemi-Kebria M, Simpkins F. Paclitaxel, carboplatin, and bevacizumab in advanced and recurrent endometrial carcinoma. Int J Gynecol Cancer. 2017;27(3):452–8.
58. Aghajanian C, Filiaci V, Dizon DS, Carlson JW, Powell MA, Secord AA, et al. A phase II study of frontline paclitaxel/carboplatin/bevacizumab, paclitaxel/carboplatin/temsirolimus, or ixabepilone/carboplatin/bevacizumab in advanced/recurrent endometrial cancer. Gynecol Oncol. 2018;150(2):274–81.
59. Viswanathan AN, Lee H, Berkowitz R, Berlin S, Campos S, Feltmate C, et al. A prospective feasibility study of radiation and concurrent bevacizumab for recurrent endometrial cancer. Gynecol Oncol. 2014;132(1):55–60.
60. Viswanathan AN, Moughan J, Miller BE, Xiao Y, Jhingran A, Portelance L, 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.
61. Tsuda H, Yamamoto K, Inoue T, Uchiyama I, Umesaki N. The role of p16-cyclin d/CDK-pRb pathway in the tumorigenesis of endometrioid-type endometrial carcinoma. Br J Cancer. 2000;82(3):675–82.
62. Oza AM, Eisenhauer EA, Elit L, Cutz JC, Sakurada A, Tsao MS, et al. Phase II study of erlotinib in recurrent or metastatic endometrial cancer: NCIC IND-148. J Clin Oncol. 2008;26(26):4319–25.

63. Bender D, Sill MW, Lankes HA, Reyes HD, Darus CJ, Delmore JE, et al. A phase II evaluation of cediranib in the treatment of recurrent or persistent endometrial cancer: an NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol. 2015;138(3):507–12.
64. Shu CA, Pike MC, Jotwani AR, Friebel TM, Soslow RA, Levine DA, et al. Uterine cancer after risk-reducing salpingo-oophorectomy without hysterectomy in women with BRCA mutations. JAMA Oncol. 2016;2(11):1434–40.
65. English DP, Roque DM, Santin AD. HER2 expression beyond breast cancer: therapeutic implications for gynecologic malignancies. Mol Diagn Ther. 2013;17(2):85–99.
66. Mentrikoski MJ, Stoler MH. HER2 immunohistochemistry significantly overestimates HER2 amplification in uterine papillary serous carcinomas. Am J Surg Pathol. 2014;38(6):844–51.
67. Jewell E, Secord AA, Brotherton T, Berchuck A. Use of trastuzumab in the treatment of metastatic endometrial cancer. Int J Gynecol Cancer. 2006;16(3):1370–3.
68. 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(2):128-31.
69. Fleming GF, Sill MW, Darcy KM, McMeekin DS, Thigpen JT, Adler LM, 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.
70. Leslie KK, Sill MW, Lankes HA, Fischer EG, Godwin AK, Gray H, et al. Lapatinib and potential prognostic value of EGFR mutations in a Gynecologic Oncology Group phase II trial of persistent or recurrent endometrial cancer. Gynecol Oncol. 2012;127(2):345–50.
71. Fader AN, Roque DM, Siegel E, Buza N, Hui P, Abdelghany O, et al. Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. J Clin Oncol. 2018;36(20):2044–51.
72. Udall M, Rizzo M, Kenny J, Doherty J, Dahm S, Robbins P, et al. PD-L1 diagnostic tests: a systematic literature review of scoring algorithms and test-validation metrics. Diagn Pathol. 2018;13(1):12.
73. Makker V, Green AK, Wenham RM, Mutch D, Davidson B, Miller DS. New therapies for advanced, recurrent, and metastatic endometrial cancers. Gynecol Oncol Res Pract. 2017;4:19.
74. Santin AD, Bellone S, Buza N, Choi J, Schwartz PE, Schlessinger J, et al. Regression of chemotherapy-resistant polymerase ε (POLE) ultra-mutated and MSH6 hyper-mutated endometrial tumors with nivolumab. Clin Cancer Res. 2016;22(23):5682–7.
75. Ott PA, Bang YJ, Berton-Rigaud D, Elez E, Pishvaian MJ, Rugo HS, et al. Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1-positive endometrial cancer: results from the KEYNOTE-028 study. J Clin Oncol. 2017;35(22):2535–41.
76. Popat S, Hubner R, Houlston RS. Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol. 2005;23(3):609–18.
77. Buecher B, Cacheux W, Rouleau E, Dieumegard B, Mitry E, Lièvre A. Role of microsatellite instability in the management of colorectal cancers. Dig Liver Dis. 2013;45(6):441–9.
78. Tannergård P, Lipford JR, Kolodner R, Frödin JE, Nordenskjöld M, Lindblom A. Mutation screening in the hMLH1 gene in Swedish hereditary nonpolyposis colon cancer families. Cancer Res. 1995;55(24):6092–6.
79. Moreira L, Balaguer F, Lindor N, de la Chapelle A, Hampel H, Aaltonen LA, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA. 2012;308(15):1555–65.
80. Wang Y, Wang Y, Li J, Cragun J, Hatch K, Chambers SK, Zheng W. Lynch syndrome related endometrial cancer: clinical significance beyond the endometrium. J Hematol Oncol. 2013;6:22.
81. Garg K, Soslow RA. Lynch syndrome (hereditary non-polyposis colorectal cancer) and endometrial carcinoma. J Clin Pathol. 2009;62(8):679–84.
82. Dudley JC, Lin MT, Le DT, Eshleman JR. Microsatellite instability as a biomarker for PD-1 blockade. Clin Cancer Res. 2016;22(4):813–20.
83. Howitt BE, Shukla SA, Sholl LM, Ritterhouse LL, Watkins JC, Rodig S, et al. Association of polymerase e-mutated and microsatellite-instable endometrial cancers with neoantigen load,

number of tumor-infiltrating lymphocytes, and expression of PD-1 and PD-L1. JAMA Oncol. 2015;1(9):1319–23.
84. Yamashita H, Nakayama K, Ishikawa M, Nakamura K, Ishibashi T, Sanuki K, et al. Microsatellite instability is a biomarker for immune checkpoint inhibitors in endometrial cancer. Oncotarget. 2017;9(5):5652–64.
85. Le DT, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372(26):2509–20.
86. Boyiadzis MM, Kirkwood JM, Marshall JL, Pritchard CC, Azad NS, Gulley JL. Significance and implications of FDA approval of pembrolizumab for biomarker-defined disease. J Immunother Cancer. 2018;6(1):35.
87. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm
88. Prescribing information: Pembrolizumab 2017. Available at http://bit.ly/2cTmltE
89. Makker V, Rasco D, Vogelzang NJ, Brose MS, Cohn AL, Mier J, et al. Lenvatinib plus pembrolizumab in patients with advanced endometrial cancer: an interim analysis of a multicentre, open-label, single-arm, phase 2 trial. Lancet Oncol. 201. https://doi.org/10.1016/S1470-2045(19)30020-8.
90. https://immuno-oncologynews.com/2018/08/14/lenvima-keytruda-combo-granted-fda-breakthrough-therapy-designation/?amp

Immunotherapy in Endometrial Cancer: An Evolving Therapeutic Modality

13

Satinder Kaur and H. S. Darling

13.1 Introduction

Endometrial adenocarcinoma (EC) is the commonest gynecologic malignancy in developed countries [1]. Endometroid histology is most common, presents at an early stage, and has a favorable prognosis. Less common variants (e.g., serous, clear cell) have much poorer prognosis. Non-metastatic endometrial carcinoma is treated with a curative intent. Clear guidelines exist for its treatment for various histologies, grades, and stages. Metastatic or recurrent EC has a bad prognosis, with limited treatment options, poor response, and grim survival. Treatment is usually palliative. Therefore, the approach should be individualized [2].

13.2 Current Treatment Paradigm

Prognosis in advanced disease is poor, with a 5-year survival of less than 50% and 20% for patients with nodal metastases and distant metastases, respectively, as compared to 95% for patients with uterus limited disease [1, 2]. There is no standardized treatment option in advanced disease. Second-line regimens have very limited activity [3, 4]. Since the completion of Gynecologic Oncology Group (GOG) protocol 177, which explored the triplet regimen of paclitaxel, doxorubicin and cisplatin (TAP) in patients with advanced-stage and recurrent EC, demonstrating an overall response rate (ORR) of 57 % and median overall survival (OS) of 15.3 months, results have been clinically disappointing [5]. GOG 209 showed 51% ORR with taxane and platinum versus TAP, and 37% versus 40% median OS, respectively [6].

S. Kaur (✉)
Gyne Oncology, Dharamshila Narayana Superspeciality Hospital, Delhi, India

H. S. Darling
Narayana Superspeciality Hospital, Gurugram, Haryana, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_13

In subsequent line therapy, various targeted agents (bevacizumab, aflibercept, temsirolimus, brivanib, cediranib) have shown an ORR of 0–24.5 % in GOG 229 [7]. Hormonal agents have 18–34% response rates (RR), and taxanes alone 20% [8, 9]. Considering this data, exploration of novel therapeutic approaches is warranted in this patient population. This review focusses on the endeavors of the scientific industry in clinical development of immune checkpoint inhibitors in advanced and recurrent disease in light of the role of tumor microenvironment.

13.3 Basics of Immunotherapy

The perplexing relationship between immunology and oncology dates back to the late nineteenth century, when William Coley invented that injecting killed bacteria into sarcoma could shrink the tumor [10]. Cytokines, checkpoint inhibitors, CAR-T cells or vaccines are the various forms of immunotherapy being tested and used in different cancers. Immune checkpoint inhibitors are the drugs being tried in endometrial cancer. Immune checkpoints refer to a controller mechanism developed by the immune system to maintain self-tolerance and minimize collateral damage during physiologic responses to pathogens. These act as logical targets for monoclonal antibodies. Cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death protein-1 (PD-1) were the first, and remain the most relevant immune-checkpoint receptors to be clinically targeted. Both belong to CD28 family of T lymphocyte receptors but are implicated in different immune-regulatory pathways. CTLA-4 acts in secondary lymphoid organs, whereas PD-1 acts within T cells, B cells, and NK cells. PD-1 is an inhibitory molecule that binds to the PD-L1 and PD-L2. PD-L1 is a ligand expressed on the surface of many tumor cells and hematopoietic cells; PD-L2 is more restricted to hematopoietic cells. The PD-1:PD-L1/2 binding downregulates immune function by switching off tumor apoptosis, promoting peripheral T suppressor cell conversion to regulatory T (Treg) cells [11, 12] (Fig. 13.1). Cytokines such as IFN gamma and IL-12 upregulate immune checkpoint receptor–ligand interaction, applying a physiologic brake on cytotoxic T cells. Based upon proven response and survival benefits, various antibodies, inhibiting PD-1 (pembrolizumab, nivolumab) and PD-L1 (atezolizumab, avelumab, durvalumab) have been approved for a number of clinical indications and are being evaluated in multiple other malignancies [13].

13.4 Molecular Classification of Endometrial Cancer

EC is heterogeneous in terms of histology, pathogenesis, prognosis, and drug sensitivity [14]. According to Bokhman's dualistic model, previously EC was classified into Type I and Type II, as per clinical, histology, and hormone receptor (HR) status. EC type I, estrogen-dependent endometroid, constituted two-third of all cases [15] and usually has good prognosis (median 5-year survival, 85.6%). Major molecular alterations of type-I carcinomas include PTEN silencing, PIK3CA mutations, MMR defects, MSI and K-RAS or β-catenin (CTNNB) mutations. Type II EC,

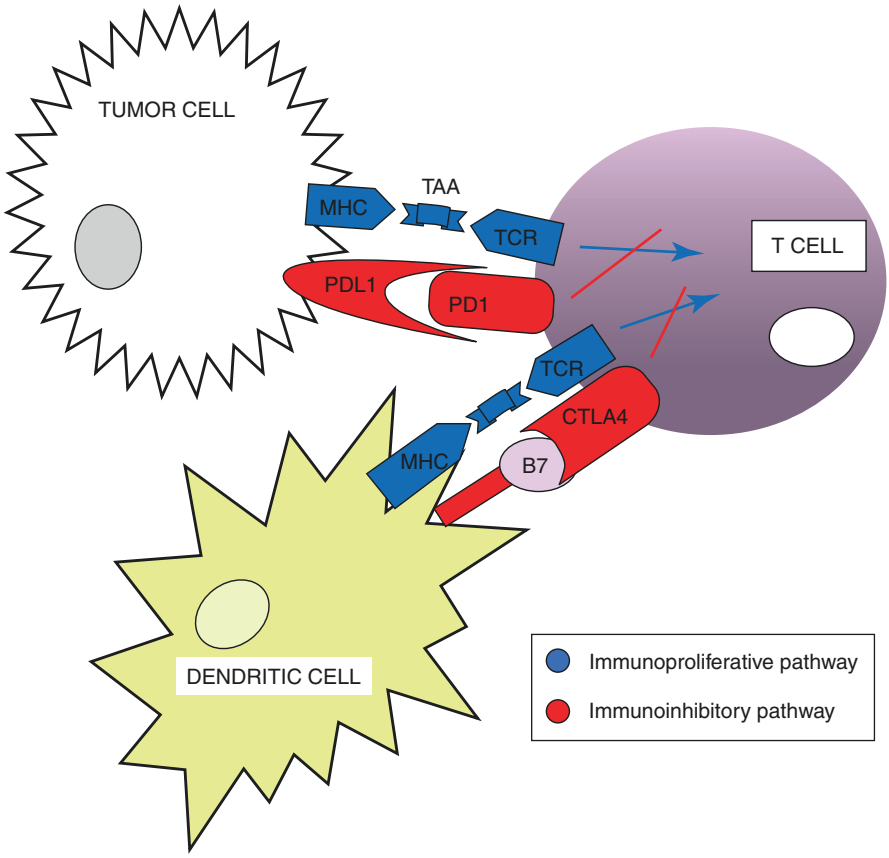


Fig. 13.1 Basis of immunotherapy. *CTLA4* cytotoxic T lymphocyte antigen 4, *MHC* major histocompatibility complex, *PDL1* programmed death receptor–ligand 1, *TAA* tumor-associated antigen, *TCR* T cell receptor

estrogen-independent, non-endometroid, comprises Grade 3 endometrioid, serous, or clear cell HR negative cancers. It is usually associated with endometrial atrophy and often shows p53 mutations, p16 inactivation, low E-cadherin expression, Her-2/neu overexpression, STK15 amplification, and loss of heterozygosity (LOH) on multiple chromosomes. Type II EC presents at an advanced stage, responds poorly to therapies, and has a worse survival rate [16–18]. In the light of new genomic and transcriptomic characterization of EC by 2013 TGCA (The Cancer Genome Atlas Research Network), this model has recently been restructured [19]. Four subtypes are recognized:

1. POLE-ultra-mutated malignancies: POLE gene encodes the catalytic subunit of DNA polymerase epsilon, a DNA repair enzyme. Somatic mutations in the exonuclease domain of POLE are characteristic of this variant. They comprise 6.4% of low-grade and 17.4% of high-grade endometrioid tumors and have a high mutation rate (232 × 10^6 mutations/Mb). Loss of function of POLE leads to

accumulation of a high frequency of C>A transversions, microsatellite stability (MSS), PTEN, PIK3R1, PIK3CA, and RAS mutations. Despite the histological grade, this group portends a good prognosis [20].

2. MSI-hyper-mutated (MSI-H): These comprise 28.6% of low-grade and 54.3% of high-grade endometrioid EC. Both hereditary and sporadic cases form a part of this category. They show MSI and a high mutation rate (18×10^6 mutations/Mb). PTEN, RPL22 frameshift deletions, and KRAS mutations are also present in some cases.
3. Copy number low EC: It is characterized by a low mutation rate (2.9×10^6 mutations/Mb) and MSS. It is generally a low-grade endometrioid cancer, comprising 60% of low-grade and 8.7% of high-grade EC. PTEN and PIK3CA are mutated in 77% and 53% of patients, respectively. WNT-B catenin mutations are also common, and RAS mutation is rare. This group has high progesterone receptor (PgR) levels, anticipating the role of endocrine modalities. Prognosis is similar to MSI-H tumors without a clear correlation between this subtype and clinical outcome [21].
4. Copy number high serous-like: It includes mainly serous and mixed histology tumors with some high-grade endometrioid EC. It has a low mutation rate (2.3×10^6 mutations/Mb) and a small load of copy number aberrations. TP53 is commonly mutated (92%), but KRAS and PTEN mutations are rare. ERBB2-amplification is seen in 25% of cases. Prognosis of these patients is poor. These new subgroups represent a step toward redefining the prognosis of EC patients and may evoke better clinical trial design with targeted agents [22].

Healthy endometrium has a specialized immune system, coping with the dual challenge of protecting against exogenous pathogens while allowing the development of an allogeneic fetus. The slowness in deciphering the complex molecular milieu of endometrium is plausible, due to the fluctuations in its immune cell composition resulting from hormonal variations [23, 24]. Sex hormones regulate this by modulating the TME. Immune cells recognize tumor-specific antigens (TSA) and tumor-associated antigens (TAA) and eliminate cancer cells [25]. Usually, immune response activation has two components, working in unison. The first one is the interaction between MHC molecules and T cell receptors (TCR); the second one is the connection of the co-stimulatory receptor CD28, present on T cells' surface, with its ligand B7 on APCs. CTLA-4 is a competitive inhibitor for binding B7, to avoid autoimmune reaction [25]. This negative feedback is mostly represented within secondary lymphoid organs. In tumors, this inhibitory pathway is the connection between PD-1 receptor on the T cells, and the PD-L1 and PD-L2 on the tumor cells surface, modulated through the local inflammatory cytokines, silencing the T cell response. This PD-1 and PDL1 over-expression creates "adaptive immune resistance" [26]. Immunohistochemical analyses performed by Vanderstraeten et al. demonstrate that 83% of primary endometrial tumors and 100% of metastatic endometrial tumors express PD-L1 [27]. Moreover, he also analyzed other immune-related molecules and reported that B7-H4, responsible for another inhibitory pathway of CD4+ and CD8+ T cells, is present in 90% of EC specimens, while IDO is expressed only in 21% of EC samples [27]. These findings confirm an important

role of PD-1/PD-L1 pathway and suggest B7-H4 signal as a potential new therapeutic target. In melanoma and NSCLC, while significantly higher response to immune checkpoint modulators is observed in tumors with high PDL1 positivity, a small subset of patients with low PD-L1 expression also benefited from anti-PD-1 or PD-L1 therapies [28]. However, high PDL1 is associated with a worse outcome in some tumors, like non-small cell lung cancer (NSCLC), kidney and bladder, but good outcome in melanoma [29]. This highlights the complex nature of this biomarker. Currently, PD-L1 is routinely analyzed in advanced NSCLC in order to prescribe checkpoint inhibitors, even when it is still controversial which is the best cutoff to define positivity and which the best antibody is to detect the expression on immunohistochemistry (IHC) assay. PD-L1 detection is regularly used also in the treatment of kidney and bladder cancers [29].

13.5 Tumor Microenvironment

The malignant cells, immune cells, activation and inhibitory molecular pathways, and the local cytokine milieu of the tumor, collectively constituting tumor microenvironment (TME), significantly impact the prognosis. EC with POLE mutation or MSI-H tumors can carry 10–100 times more mutations as compared to the MSS tumors [19]. High tumor mutational burden (TMB) can harbor potent neo-antigens and invite host immune surveillance, resulting in improved prognosis. PD-1 and PD-L1 are more frequently observed in POLE-mutated and MSI-H tumors [30]. This imparts more aggressive histopathologic features, albeit, they have a good prognosis owing to high number of CD3+ and CD8+ tumor-infiltrating lymphocytes (TILs) limiting disease dissemination. de Jong et al. analyzed a number of EC patients and detected that the presence of high CD8+ TILs was an independent predictor of increased overall survival (OS) and that the presence of a high CD8+/FoxP3+ ratio was an independent predictor of increased disease free survival (DFS) in type I, though not type II EC [31]. T-reg cells are a type of CD4+ T cells that inhibit immune responses characterized by lack of expression of effector cytokines, such as interferon (IFN)-γ and the production of inhibitory cytokines, such as transforming growth factor (TGF)-β, interleukin (IL)-10, and IL-35 [32]. The TransPORTEC consortium analyses on 116 high-risk ECs, published in 2017, confirmed that POLE-mutant and MSI-H tumors have higher numbers of tumor-infiltrating T cells. Also, owing to huge density of PD-1 and PD-L1 expression, they should be the perfect candidates for immune checkpoint inhibitors [33]. In order to suppress the activation of the inhibitory pathways described above different antibodies have been developed.

13.6 Rationale of Immunotherapy in Endometrial Cancer

The most relevant considerations concerning the role of immune-checkpoint inhibitors in EC might be identifying the subset most likely to respond to immunotherapy, the biomarkers most likely to predict response, and the therapy combinations most likely to enhance drug performance while limiting toxicity. Limited clinical studies

are available on the use of checkpoint inhibition in EC. The growing recognition that MSI may serve as a surrogate biomarker for response to immunotherapy has led to studies conduction in this direction. EC is a tumor marked by diverse grade and histology with significant subsets harboring high mutational burdens in concert with MSI [19]. Higher number of mutation-associated neoantigens resulting MSI-H (>20 times) as compared to MSS render enhanced anti-PD-1 responsiveness of this genetically predefined subset [34]. In the study focusing on evaluating the expression of PD-L1 and B7-H4, as well as the MSI status in a cohort of endometrial tumors, using IHC staining and analysis of RNA expression, high levels of PD-L1 and B7-H4 expression were seen. B7-H4 levels were not specific for any tumor type; however, high prevalence of PD-L1 positivity was observed in low-grade endometrioid MSI-high cohort. This data is consistent with high levels of PD-L1 expression in MSI-high colorectal cancers. Also, high expression of PD-L1 correlated with a lymphocyte infiltration index [33]. PD-1 has garnered particular interest as an immune-related therapeutic target, highlighting its vital role in tumor immune evasion. The interaction of PD-L1 with PD-1, which is expressed on TILs, can lead to their functional inactivation and prevent T cell-mediated tumor cytolysis. Blocking this interaction with monoclonal antibodies directed against PD-1 or PD-L1 can result in objective tumor responses, many of which are durable, in a wide spectrum of cancers [35]. Collectively, these data suggest that immune modulation is an important mechanism for significant subsets of EC, one that may be exploited through therapeutic inhibition of PD-L1 and possibly other.

13.7 Evidence for Role of Immunotherapy in EC

13.7.1 Completed and Preliminary Reported Trials (Table 13.1)

The first evidence for the role of immunotherapy in EC emanates from a phase II trial on 41 colorectal and other cancers, including two EC patients, published in 2015 by Le et al. They found a higher immune-related ORR and 20-week immune-related PFS, 40% and 78%, respectively, in the MMR deficient cohorts, versus 0 and 11% in MMR proficient colorectal patients. In the cohort including the two MMR-deficient EC patients, immune-related ORR and PFS were 71% and 67%, respectively [34]. This study was a first pointer toward possible connection between TME, genotype, and response to checkpoint inhibitors. Results of KEYNOTE-028, a phase Ib trial of 24 advanced EC patients, recently reported by Ott and colleagues, showed response to Pembrolizumab 10 mg/kg every 2 weeks for up to 24 months. ORR was 13%, with three patients obtaining a PR. SD was seen in other three patients. Six-months PFS and OS rates of 19.0% and 68.8% were seen, respectively. About half of the patients (54%) suffered drug-related adverse events; most common being pruritus, asthenia, fatigue, pyrexia, and anorexia. No patients died or discontinued Pembrolizumab because of toxicities [36]. One patient from this trial showed rapid improvement once pembrolizumab was initiated, exhibiting a PR after 8 weeks and sustaining the response for more than 14 months. Genomic

Table 13.1 Preliminary reported and published immunotherapy trials in advanced EC

NCT number/name	Population	Intervention	Phase/*n*	Completion date
NCT02054806	Advanced solid tumors	Pembrolizumab	1/477	August 13, 2019
NCT02501096	Selected solid tumors	Lenvatinib + Pembrolizumab	1&2/329	February 29, 2020
NCT01375842	Advanced malignancies	Atezolizumab	1/661	September 30, 2018

profiling revealed that the patient had a POLE mutation. This postulates that the presence of POLE mutations may aid in identifying pembrolizumab responsive patients [37]. Makker et al. have presented the results of a phase I/II trial of 23 metastatic EC patients receiving Lenvatinib 20 mg/day and Pembrolizumab 200 mg every 3 weeks. The reported ORR was 48% and a DCR of 96%. The most common adverse events were hypertension, fatigue, arthralgia, diarrhea, and nausea [38]. In 2016, Santin and colleagues reported two cases of recurrent chemotherapy-refractory EC, treated with the anti-PD-1, Nivolumab. One woman had a mixed clear cell and endometrioid POLE-mutated EC and the other had a serous MSH6 mutated EC. Nivolumab 3 mg/kg biweekly was the treatment schedule. CTL infiltration and PD-L1 expression were evaluated on a pretreatment biopsy. Both had a moderate amount of TILs. PD-L1 expression was 5% in the first case and, while none in the second. p53 by IHC was a wild-type pattern. Both patients showed a persistent clinical response at 7 and 9 months and no severe toxicities were reported [39].

PD-L1 antibodies have also been tested in various studies. Fleming et al. tested Atezolizumab 15 mg/m^2 every 3 weeks, in a phase Ia trial of 15 EC patients. Seven patients were MSS, seven MSI unknown, and only one patient had an MSI-H. One-third of patients had PD-L1 $\geq$5% on immune cells while in the remaining 67% the PD-L1 expression was lower. Two patients obtained a PR and other two achieved an SD with an ORR of 13% and a DCR of 27%. Both responders had high PD-L1, while dense TILs in one having MSI-S disease, and moderate TILs in the other with MSI-H. The duration of response was 7.3 and 8.1+ months, respectively. Median PFS was 1.7 months and a median OS of 9.6 months was achieved. Severe drug-related adverse events (colitis and rash) occurred only in two patients, but none had G4-5 toxicities [40]. Next possible target for checkpoint inhibition is CTLA-4. Ipilimumab and Tremelimumab have proven efficacy melanoma but they need to be tested in EC.

13.7.2 Ongoing Trials

Multiple trials are in progress to demonstrate the efficacy of immune checkpoint inhibitors alone or in combination with cytotoxic chemotherapy in EC. A phase 2 trial, NCT02912572, with an anti-PD-L1 antibody Avelumab, is an open-label, two-stage study of Avelumab 10 mg/kg biweekly to women with recurrent or persistent EC. Cohorts formation is on the basis of the MMR proteins expression. Co-primary

Table 13.2 Ongoing immunotherapy trials in advanced EC

NCT number/ name	Population	Intervention	Phase/*n*	Completion date
NCT02912572	MSS, MSI-H, and POLE mutated EC	Avelumab	2/70	April 2024
NCT03603184 (AtTEnd)	Advanced EC	CT+/– Atezolizumab	3/550	July 2022
NCT03277482	Recurrent gynecological cancers	Durvalumab, tremelimumab, RT	1/32	November 2020
NCT03276013 (TOPIC)	Advanced EC	Pembrolizumab+ doxorubicin	2/51	May 2020
NCT03241745	MSI-H EC	Nivolumab	2/40	August 2020

endpoints are ORR and the rate of PFS at 6 months. PHAEDRA is a phase II trial in chemotherapy-refractory EC, testing the efficacy and tolerability of Durvalumab. AtTEnd is a phase III trial comparing the standard of care, Paclitaxel/carboplatin-based cytotoxic chemotherapy with or without Atezolizumab in advanced EC. A list of a few ongoing trials of immune-checkpoint inhibitors in advanced EC is presented in Table 13.2.

13.8 What Can We Expect?

EC is a disease of the elderly women. By the time it received attention of immunotherapy researchers, molecular science has become even more complex. From the teething days of immunotherapy in EC, the former has to juggle with a number of molecular markers viz, MSI, TME, TILs, PDL-1, B7-H4, and so forth. With so much of molecular knowledge, on the background of new classification of EC, newer trials are being planned for subgrouping the patients according to the expected response to immune checkpoint inhibitors. Although it is a slow journey, we definitely expect to zero-in on to the intended subset, presumably, the best candidate for immunotherapy.

13.9 Future Perspectives

Personalized, gene-directed, targeted therapy is the way forward. With the advent of the role of trastuzumab in advanced serous EC, the interest has risen to locate other such targets, which can be hit to improve the quality and quantity of EC patients lives, for which at present, we have meager to be offered. It would be a dream come true if it can acquire a position in frontline setting, where cytotoxic chemotherapy is cumbersome to administer. More well-planned clinical trials are needed to gather data regarding molecular manipulation of targeted therapy, which can be

implemented in a personalized fashion. Apart from zooming in on to the newer systemic therapies, loco-regional therapies for the locally advanced or recurrent subset also need to be improved, which may lessen the occurrence of local and metastatic relapses. Local therapies combined with molecular data, with the addition of newer targeted molecules is the arena yet to be explored. Future studies must try to focus on this relatively blind spot.

13.10 Summary

Advanced metastatic cancer can present de novo, or after failure of earlier therapies. There is a limited arsenal to treat this entity, which constitutes the most common gynecological malignancy in developed countries and the second most common (first being cervical cancer) in developing countries. As of now, we do not have sufficient evidence to exploit immunotherapy in the field of EC, which we are rapidly achieving in other cancers. Immunotherapy in EC is evolving; the current role is very much restricted to a subset of patients. Presently, pembrolizumab is broadly FDA approved for MSI-H solid cancers, including EC. Further more robust data is required for its expanded use.

13.11 Key Points

1. Molecular classification of EC includes type-I carcinomas having PTEN silencing, PIK3CA mutations, MMR defects, MSI and K-RAS or β-catenin (CTNNB) mutations. Type II EC is usually associated with p53 mutations, p16 inactivation, low E-cadherin expression, Her-2/neu overexpression, STK15 amplification, and loss of heterozygosity (LOH) on multiple chromosomes.
2. The malignant cells, immune cells, activation and inhibitory molecular pathways, and the local cytokine milieu of the tumor, collectively constitutes tumor microenvironment (TME), which significantly impacts the prognosis.
3. POLE-mutant and MSI-H tumors have higher numbers of tumor-infiltrating T cells and a huge density of PD-1 and PD-L1 expression, which makes them the perfect candidates for immune checkpoint inhibitors.
4. PD-1 has garnered particular interest as an immune-related therapeutic target, highlighting its vital role in tumor immune evasion. Blocking the interaction between PD-L1 with PD-1 can result in objective tumor responses, many of which are durable, in a wide spectrum of cancers.

References

1. Dowdy SC. Improving oncologic outcomes for women with endometrial cancer: realigning our sights. Gynecol Oncol. 2014;133:370–4.

2. National Cancer Institute: SEER Stat Fact Sheets: Endometrial Cancer. http://seer.cancer.gov/statfacts/html/corp.html. Accessed 23 Aug 2015.
3. National Comprehensive Cancer Network: Clinical Practice Guidelines for Uterine Neoplasms, Version2, 2019. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf
4. Moxley KM, McMeekin DS. Endometrial carcinoma: a review of chemotherapy, drug resistance, and the search for new agents. Oncologist. 2010;15:1026–33.
5. Fleming GF, Brunetto VL, Cella D, Look KY, Reid GC, Munkarah AR, 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(11):2159–66. https://doi.org/10.1200/JCO.2004.07.184.
6. Miller DS, Filiaci G, Mannel R, et al. Randomized phase III noninferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group Study. LBA2. Presented at the 2012 Society of Gynecologic Oncology Annual Meeting, Austin, TX.
7. Longoria TC, Eskander RN. Immunotherapy in endometrial cancer—an evolving therapeutic paradigm. Gynecol Oncol Res Pract. 2015;2(1):11. https://doi.org/10.1186/s40661-015-0020-3
8. Pectasides D, Pectasides E, Economopoulos T. Systemic therapy in metastatic or recurrent endometrial cancer. Cancer Treat Rev. 2007;33(2):177–90. https://doi.org/10.1016/j.ctrv.2006.10.007.
9. Dizon DS. Treatment options for advanced endometrial carcinoma. Gynecol Oncol. 2010;117(2):373–81. https://doi.org/10.1016/j.ygyno.2010.02.007.
10. Coley WB. The treatment of malignant tumors by repeated inoculations of erysipelas: with a report of ten original cases. Am J Med Sci. 1893;105:487.
11. Francisco LM, Salinas VH, Brown KE, et al. PD-L1 regulates the development, maintenance, and function of induced regulatory T cells. J Exp Med. 2009;206:3015.
12. Amarnath S, Mangus CW, Wang JC, et al. The PDL1-PD1 axis converts human TH1 cells into regulatory T cells. Sci Transl Med 2011; 3:111ra120.
13. Walker LS, Sansom DM. The emerging role of CTLA4 as a cell-extrinsic regulator of T cell responses. Nat Rev Immunol. 2011;11:852.
14. Espinosa I, D'Angelo E, Palacios J, Prat J. Mixed and ambiguous endometrial carcinomas: a heterogenous group of tumors with different clinicopathologic and molecular genetic features. Am J Surg Pathol. 2016;40:972–81. https://doi.org/10.1097/pas.0000000000000640
15. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15:10–7.
16. Matias-Guiu X, Catasus L, Bussaglia E, Lagarda H, Garcia A, Pons C, Muñoz J, Argüelles R, Machin P, Prat J. Molecular pathology of endometrial hyperplasia and carcinoma. Hum Pathol. 2001;32:569–77.
17. Moreno-Bueno G, Sánchez-Estévez C, Cassia R, Rodríguez-Perales S, Díaz-Uriarte R, Domínguez O, Hardisson D, Andujar M, Prat J, Matias-Guiu X, Cigudosa JC, Palacios J. Differential gene expression profile in endometrioid and nonendometrioid endometrial carcinoma: STK15 is frequently overexpressed and amplified in nonendometrioid carcinomas. Cancer Res. 2003;63:5697–702.
18. Yalta T, Atay L, Atalay F, Caydere M, Gonultas M, Ustun H. E-cadherin expression in endometrial malignancies: comparison between endometrioid and non-endometrioid carcinomas. J Int Med Res. 2009;37:163–8.
19. Cancer Genome Atlas Research Network, Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, Yau C, Laird PW, Ding L, Zhang W, Mills GB, Kucherlapati R, Mardis ER, Levine DA. Integrated genomic characterization of endometrial carcinoma. Nature. 2013; 497: 67–73.
20. Gargiulo P, Della Pepa C, Berardi S, Califano D, Scala S, Buonaguro L, Ciliberto G, Brauchli P, Pignata S. Tumor genotype and immune microenvironment in POLEultramutated and MSI-hypermutated Endometrial Cancers: new candidates for checkpoint blockade immunotherapy? Cancer Treat Rev. 2016;48:61–8. https://doi.org/10.1016/j.ctrv.2016.06.008
21. Le Gallo M, Bell DW. The emerging genomic landscape of endometrial cancer. Clin Chem. 2014; 60:98–110. https://doi.org/10.1373/clinchem.2013.205740 .

22. Kandoth C, Schultz N, Cherniack AD, Akbani R, Liu Y, Shen H, Robertson AG, Pashtan I, Shen R, Benz CC, Yau C, Laird PW, Ding L, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013; 497:67–73. https://doi.org/10.1038/nature12113 .
23. Wira CR, Fahey JV, Ghosh M, Patel MV, Hickey DK, Ochiel DO. Sex hormone regulation of innate immunity in the female reproductive tract: the role of epithelial cells in balancing reproductive potential with protection against sexually transmitted pathogens. Am J Reprod Immunol. 2010; 63(6):544–65. https://doi.org/10.1111/j.1600-0897.2010.00842.x.
24. Vanderstraeten A, Tuyaerts S, Amant F. The immune system in the normal endometrium and implications for endometrial cancer development. J Reprod Immunol. 2015;109:7–16. https://doi.org/10.1016/j.jri.2014.12.006.
25. Koebel CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, Old LJ, Smyth MJ, Schreiber RD. Adaptive immunity maintains occult cancer in an equilibrium state. Nature. 2007;450:903–7. https://doi.org/10.1038/nature06309
26. Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, Chmielowski B, Spasic M, Henry G, Ciobanu V, West AN, Carmona M, Kivork C, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014; 515:568–71. https://doi.org/10.1038/nature13954.
27. Vanderstraeten A, Luyten C, Verbist G, et al. Mapping the immunosuppressive environment in uterine tumors: implications for immunotherapy. Cancer Immunol Immunother. 2014;63:545–57.
28. T. Zhang, J. Xie, S. Arai, L. Wang, X. Shi, N. Shi, et al. The efficacy and safety of anti-PD-1/PD-L1 antibodies for treatment of advanced or refractory cancers: a metaanalysis. Oncotarget. 2016; 7(45):73068–79.
29. Mittica G, Ghisoni E, Giannone G, Aglietta M, Genta S, Valabrega G. Checkpoint inhibitors in endometrial cancer: preclinical rationale and clinical activity. Oncotarget. 2017;8(52):90532–44. https://doi.org/10.18632/oncotarget.20042.
30. Colli LM, Machiela MJ, Myers TA, Jessop L, Yu K, Chanock SJ. Burden of nonsynonymous mutations among TCGA cancers and candidate immune checkpoint inhibitor responses. Cancer Res. 2016;76(13):3767–72.
31. de Jong RA, Leffers N, Boezen HM, ten Hoor KA, van der Zee AG, Hollema H, et al. Presence of tumor-infiltrating lymphocytes is an independent prognostic factor in type I and II endometrial cancer. Gynecol Oncol. 2009;114(1):105–10. https://doi.org/10.1016/j.ygyno.2009.03.022.
32. Yamagami W, Susumu N, Tanaka H, Hirasawa A, Banno K, Suzuki N, et al. Immunofluorescence-detected infiltration of CD4 + FOXP3+ regulatory T cells is relevant to the prognosis of patients with endometrial cancer. Int J Gynecol Cancer. 2011;21(9):1628–34. https://doi.org/10.1097/IGC.0b013e31822c271f.
33. Bregar A, Deshpande A, Grange C, Zi T, Stall J, Hirsch H, et al. Characterization of immune regulatory molecules B7-H4 and PD-L1 in low and high grade endometrial tumors. Gynecol Oncol. 2017;145(3):446–52. https://doi.org/10.1016/j.ygyno.2017.03.006
34. Le DT, Uram JN, Wang H, et al. PD-1 blockade in tumors with mismatch-repair deficiency. N Engl J Med. 2015;372:2509–20.
35. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 2015;348:56–61.
36. Ott PA, Bang Y-J, Berton-Rigaud D, Elez E, Pishvaian MJ, Rugo HS, et al. Safety and antitumor activity of pembrolizumab in advanced programmed death ligand 1-positive endometrial cancer: results from the KEYNOTE-028 study. J Clin Oncol. 2017;35(22):2535–41. https://doi.org/10.1200/JCO.2017.72.5952
37. Mehnert JM, Panda A, Zhong H, Hirshfield K, Damare S, Lane K, Sokol L, Stein MN, Rodriguez-Rodriquez L, Kaufman HL, Ali S, Ross JS, Pavlick DC, et al. Immune activation and response to pembrolizumab in POLE-mutant endometrial cancer. J Clin Invest. 2016;126:2334–40. https://doi.org/10.1172/jci84940
38. Makker V, Rasco DW, Dutcus EC, Stepan DE, Li D, Schmidt EW, Shumaker RC, Taylor MH. A phase Ib/II trial of lenvatinib (LEN) plus pembrolizumab (Pembro) in patients (Pts) with endometrial carcinoma. J Clin Oncol. 2017; 35:5598.

39. Santin AD, Bellone S, Buza N, Choi J, Schwartz PE, Schlessinger J, Lifton RP. Regression of chemotherapy-resistant polymerase ε (POLE) ultra-mutated and MSH6 hypermutated endometrial tumors with nivolumab. Clin Cancer Res. 2016;22:5682–7.
40. Fleming GF, Emens LA, Eder JP, Hamilton EP, Liu JF, Liu B, Molinero L, Fasso M, O'Hear C, Braiteh FS. Clinical activity, safety and biomarker results from a phase Ia study of atezolizumab in advanced/recurrent endometrial cancer (rEC). J Clin Oncol 2017; 35:5585.

Recurrent Endometrial Cancer

14

Seema Singhal and Asmita Kaundal

14.1 Introduction

When endometrial cancer occurs more than three months after achieving complete remission (CR) following initial treatment, it is labelled as recurrent endometrial cancer (REC) [1]. The overall rate of recurrence for endometrial cancer is approximately 10–15% with more than 50% cases occurring within 2 years of primary treatment [2, 3]. Women with REC represent a heterogeneous group, with variable clinical profile and therapeutic response. Although the prognosis of endometrial cancer is largely good owing to its early detection, but the prognosis of recurrent disease remains grave, reflecting the biologically aggressive nature of recurrent disease. The role of surgery, contrary to the primary setting is not well established in REC and radiation therapy or systemic therapy plays an important role in its management. It is prudent to do a detailed counselling explaining the biological behavior of the disease and available therapeutic options prior to starting any therapy.

14.2 Factors Affecting Survival in Patients with Recurrent Endometrial Cancer

Recurrent endometrial cancer is treatable but not curable, unless recurrence is isolated and is confined to the vaginal vault [4]. Abdominal and distant metastasis are the main cause of death in women with recurrent endometrial cancer.

S. Singhal (✉) · A. Kaundal
Department of Obstetrics and Gynecology, All India Institute of Medical Sciences, New Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_14

14.3 Diagnosis of Recurrent Endometrial Cancer

Majority of recurrences are seen within 3 years of the initial diagnosis. The clinical manifestations are usually non-specific but pattern depends on the site of recurrent disease, which may be either isolated over the vault, in the pelvis or distant metastatic disease. The most common presentation is bleeding from vagina, bladder, or rectum. Other symptoms can be loss of appetite, loss of weight, pain, cough, dyspnea, or swelling in the lower limbs [5].

A thorough history taking including the symptom-free interval, detailed systemic examination, especially to rule out any nodal disease should be done. Pelvic examination along with a biopsy of any suspicious growth may help to confirm the diagnosis. Image-guided biopsy should be considered if required. The histological type, grade, and receptor status should be confirmed in the biopsy specimen. Whole-body imaging (chest, abdomen, and pelvis) is advised to confirm the extent of recurrence and to rule out metastasis. Imaging modality is decided depending on the available facility. In clinical practice, contrast-enhanced CT scan is usually the initial study to confirm the disease extent. PET-CT is usually advised for patients who are planned for surgery/ locoregional therapy or when findings of CECT are equivocal [6].

Other tests including CA-125, especially if initial reports are available, and tumor testing for hormone receptor expression (ER, PR, and HER2) should be specifically done for prognostication and planning endocrine therapy.

14.4 Management of Recurrent Endometrial Cancer

14.4.1 Principles

The choice of therapy depends on several factors. These factors are enumerated as follows:

1. Extent of residual disease after initial surgery
2. Patient's performance status
3. Site, size, and nature of recurrence
4. Type of prior adjuvant therapy
5. Disease-free interval
6. Hormone receptor status of tumor
7. Intention of treatment; curative, or palliative

The outcome of REC mainly depends on the site of recurrence, tumor grade and histology, disease-free interval, and prior treatment [7]. Women with a longer disease-free interval, well-differentiated endometrioid adenocarcinoma, and isolated vaginal recurrence have favorable prognosis with recurrent endometrial cancer [8, 9]. Women with clear cell carcinoma or serous histology are known to have poorer progression-free survival (PFS) and overall survival (OS) [10].

14.4.2 Management Options

The therapeutic options for managing REC are limited and most of the studies, have combined the primary advanced cases along with recurrent disease to assess the response of various modalities. The management options depend largely on pattern of recurrence and the modality that was used to treat the initial disease [11]. The recurrent disease generally carries a poor prognosis and the treatment response does not depend on histology unlike the new disease [10]. Women with recurrent disease may either have vault recurrence or have pelvic recurrence or metastatic disease. Women with isolated local vaginal or pelvic recurrence is potentially curable. On the other hand, the cases who have recurrence outside the pelvis or those with distant failure, cannot be cured and the intention of therapy is predominantly palliative. The therapeutic options available are as follows:

1. Surgery—Surgical management is preferred in patients with isolated vaginal vault recurrence or central pelvic recurrence or those with single metastasis.
2. Radiotherapy—In previously nonirradiated pelvis radiotherapy is a better option.
3. Systemic therapy—In women with metastatic disease or those who are not candidates for local therapeutic approach, systemic therapy is used.
4. Hormonal therapy—Hormones are used for low-grade endometrioid adenocarcinoma with positive receptor status.
5. Targeted therapy.
6. Combination therapy.

14.5 Surgery

Surgical management of recurrent disease is challenging because of generally compromised performance status (owing to the presence of multiple comorbidities) and technical difficulties due to loss of planes as a result of previous surgery or irradiation. The outcome of surgery depends on careful selection of cases and type of surgery.

The optimum surgical candidate in a recurrent setting is a woman who has isolated recurrence in previously irradiated pelvis. The recurrence rates in women who receive appropriate adjuvant therapy after surgery remain as low as 2% [12]. With recurrent disease, the available surgical options depend on the technical feasibility and patient tolerance. Two types of surgical procedures can be performed; Exenterative and Non-exenterative procedures. Residual disease after surgery is the most significant factor affecting patient survival and therefore all efforts should be made to achieve complete cytoreduction even if this necessitates multiple visceral surgeries [13]. However, patient tolerance and performance remain critical to decide the extent of resection. Very few studies have investigated the outcome of women with REC-treated surgically. A study by Bristow et al. [11] investigated the outcome of 35 women with recurrent endometrial cancer who were treated with surgery and compared their outcome with another 30 patients in whom, no surgical procedure

was done. The median survival after recurrence was 28 months in the intervention group and 13 months in the control group ($p < 0.0001$). Complete cytoreduction was achieved in 66% cases and survival was better in cases who had R0 resection ($p < 0.001$). In the surgically treated arm, no significant major postoperative complications were observed and 31% cases had only minor complications. Another series included 44 women with REC and the median OS after pelvic exenteration was 10.2 months and 5-year OS was 20%. When exenteration surgery was performed R0 resection was achievable in 55–65% cases [13–15] and 5-year OS ranged from 20 to 40% after pelvic exenteration [11]. Hence, women with metastatic recurrent disease in peritoneal cavity may be given the option of surgical cytoreduction like ovarian malignancy [11].

Survival after surgical management depends on several factors which include the site of recurrence (local pelvic or vaginal) extent of cytoreduction, tumor grade, performance status, and chemotherapy after surgery [13]. Complete cytoreduction was observed to be the most important factor affecting survival but it was achievable in 56% cases only. Median survival was 43 months for those with R0 resection and 10 months for those with residual disease >2 cm ($p < 0.01$). Similarly, in another study also survival was significantly more in women with optimal resection than suboptimal resection (53 vs. 9 months, $p < 0.05$) [10]. Although the risk of postoperative complications was as high as 8–10%, but considering the otherwise poor prognosis even these high rates may be acceptable [13].

Women with local vaginal recurrence, where resection could be achieved with free margins may be kept under close surveillance without any adjuvant treatment. On the other hand, cases with pelvic recurrence, should receive postoperative adjuvant therapy despite R0 resection because of high risk of future relapse.

14.6 Radiation

This modality is most appropriate and can be administered with a curative intention to women with local pelvic recurrence with no prior history of radiation therapy during initial treatment. Radiation therapy for isolated vaginal recurrence in a nonirradiated pelvis was associated with a 5-year OS of 53–75% [16, 17]. In PORTEC 1 trial, a cohort of 30 women who had isolated vaginal recurrence and were radiation naïve, whole pelvic RT with or without brachytherapy was administered with a curative intention and the response rates were as good as 87% [16].

Women who develop recurrence in a previously irradiated pelvis and where even surgery is not feasible conventional radiotherapy is not a viable option because of increased risk to surrounding organs. However, these cases can be considered for tailored approaches including stereotactic radiation therapy. In a study of 27 cases of REC after conventional RT, stereotactic RT was associated with a 96% symptomatic response and there were no grade 3,4 toxicities [18]. However, nonavailability of these advanced technologies in most of the centers remains the main limiting factor.

14.7 Chemotherapy

Selected cases with recurrent metastatic disease who are chemotherapy naïve and are not surgical candidates should be offered medical therapy. Treatment for these cases is usually palliative. The response rates of single-agent chemotherapy agents range from 21 to 36%; Doxorubicin 17–37%, Paclitaxel 36%, Cisplatin 20–42%, and Carboplatin 24–33%. The PFS and OS with various chemotherapeutic drugs are summarized in Table 14.1. The role of chemotherapy in women who had earlier

Table 14.1 Summary of evidence to support the role of chemotherapy

Trial	Regimen	Response rates	PFS (months)	OS (months)	Adverse effects
GOG 107 [19]	Dox (60 mg/m^2)+ Cis (50 mg/m^2) vs Dox (60 mg/m^2) Every 3 weeks till PD or maximum dose of Doxo (500 mg/m^2) or unacceptable toxicity	45% vs. 27%	5.7 vs. 3.8	9.0 vs. 9.2	More Gr-3/4 hematological adverse effects with combination therapy
EORTC 55872 [20]	Dox (60 mg/m^2) + Cis (50 mg/m^2) vs Dox (60 mg/m^2) Every 4 weeks	43% vs. 17%	8 vs. 7	9 vs. 7	Higher but acceptable toxicity in combination arm
GOG 163 [21]	Dox+Cis vs Pac+Dox	40% vs. 44%	7.2 vs. 6.0	12.4 vs. 13.6	
GOG 177 [22]	(Two-drug) Dox (60 mg/m^2) + Cis(50 mg/m^2) vs (Three drug) **Day-1** Dox (45 mg/m^2)+Cis (50 mg/m^2) **Day-2** Pac (160 mg/m^2) with Filgrastim Every 3 weeks till maximum of 7 cycles	34% vs. 57%	5.3 vs. 8.3	12.1 vs. 15.3	Increased neurological toxicity with three drug regimen
GOG 209 [23]	Carb + Pac vs. Dox + Cis + Pac 3 weekly, 7 cycles	51% in each arm	13 in each arm	37 vs. 40	lower incidence of grade 2/3 sensory neuropathy (19 vs. 26%), vomiting (4% vs. 7%), loose stools (2% vs. 6%), metabolic derangements (8% vs. 14%) in TP

Dox doxorubicin, *Carb* carboplatin, *Cis* cisplatin, *Pac* paclitaxel

received cytotoxic chemotherapy during primary management is limited [2]. Table 14.1 depicts the summary of phase III RCTs conducted in advanced (stage III and IV) and relapsed endometrial cancer.

The first-line therapy for those with metastatic disease, remains Platinum-based combination therapy either TP (Carboplatin + Paclitaxel) or the triple drug combination regimen containing Cisplatin, Doxorubicin, and Paclitaxel (TAP). The efficacy of TP and TAP regimen is similar but the toxicity profile is better with TP regimen [14].

The options for second-line chemotherapy regimen depends on previous adverse events and patient performance status. Preferably molecular profiling should be done for all metastatic or recurrent endometrial cancers, if not done at the time of diagnosis. Commonly used agents in this setting are Liposomal Doxorubicin, Paclitaxel, Dactinomycin, Topotecan, Oxaliplatin, and Docetaxel [2]. Women who had received Paclitaxel in initial part of their management are considered good candidates for Liposomal Doxorubicin treatment.

14.8 Hormonal Therapy

Endocrine therapy may be considered as either the first-line therapy or second-line option for selected cases. This therapy has accepted toxicity profile and does not have side effects as that of chemotherapy. The side effects are generally mild and do not include grade 3 or 4 toxicity. The response mainly depends on the grade of tumor, ER-PR expression, and symptoms of patient. Women who are predominantly asymptomatic, have positive ER/PR status and disease is low grade, show favorable response to endocrine therapy. It has been seen that patients with high PR levels show superior responses than those with low levels (72% vs. 12%). Similarly, the response rates with grade 1, grade 2, and grade 3 disease were 37%, 23%, and 9%, respectively [24]. Those who lack these features should be recommended immunotherapy. Favorable response with hormonal agents is seen in approximately 15–30% cases [25].

Several agents and regimen have been investigated. However, because of scarce literature, there is no recommended preferred regimen. Lower doses are preferred over higher doses. In a GOG trial, MPA (medroxyprogesterone acetate) in a dose of 2000 mg was compared with 200 mg dose. The response rates supported low dose regimen (RR 25% vs. 15%) and the average disease-free interval was also better with low-dose regimen (3.2 vs. 2.5 months) [26]. Broadly hormonal therapy for REC can be divided into two categories, which include progestin-containing regimens and antiestrogen regimens.

(A) Progestin-containing regimens. Progesterone antagonizes the estrogen-mediated cell proliferation by increasing gene expression and the degradation of estrogen receptors in stromal tissues. In addition, progesterone also causes cell cycle arrest, has anti-inflammatory effects, blocks the invasion, and suppresses apoptosis [4].

1. Progestins alone therapy: Progestational agents including Megestrol acetate (160 mg daily) or Medroxyprogesterone acetate (200 mg daily) are the most commonly used endocrine therapy with response rates ranging from 15 to 25% [27].
2. The benefits of Megestrol acetate (80 mg twice daily) for 3 weeks alternating with Tamoxifen (40 mg twice daily) for 3 weeks has been investigated in a GOG trial and response rates as good as 27% with median OS of 14 months was observed. This regimen was found useful even for high-grade disease with 22% response rates. The mechanism of benefit of this regimen was because the sustained activation of PR might cause degradation of these receptors and addition of Tamoxifen may have caused induction of progesterone receptor expression and increasing the sensitivity to progesterone [28].

(B) Antiestrogen regimens

1. Selective estrogen receptor modulators: These agents are competitive inhibitors of estrogen receptors. Tamoxifen at the dose of 20 mg twice daily has been investigated but the overall response rate was only 10% [29].
2. Gonadotropin-releasing hormone analogues: These agents downregulate the FSH and LH receptors in pituitary leading to fall in the level of FSH and LH hormones and subsequent decrease in the level of estrogen hormones. They are associated with unsatisfactory response rates as low as 11% and thus are not widely used for treatment of REC [30].
3. Aromatase Inhibitors: These are nonsteroidal aromatase inhibitors that decrease the circulatory and intra-tumoral levels of estrogen [11]. Letrozole was associated with a median OS of 8.8 months.

14.9 Targeted Therapy

The limited efficacy of chemotherapy and better knowledge of pathogenic molecular pathways has evoked interest in targeted approach against the key drivers of mammalian target of rapamycin (mTOR), angiogenesis, and the epidermal growth factor receptor (EGFR) family as relevant therapeutic targets. Table 14.2 enlists the various therapeutic targets in the treatment of recurrent endometrial cancer.

Table 14.2 Targeted therapy options [31]

Targeted therapy	Response rates	Adverse effects
VEGFR inhibitors	15–18%	Fatigue, hypertension, diarrhea, and hematological
Multi-targeted VEGFR/ FGFR inhibitors	14–24%	Fistulae, perforation, hypertension, fatigue, and gastrointesinal toxicity
mTOR inhibitors	Alone: 10% Combined with Letrozole: 32%	
PI3K/mTOR inhibitors	9%	Hyperglycemia 45%

14.10 Combined Modalities

Several modalities combining chemotherapeutic agents and hormonal agents have been tried and the median survival in combination regimen (cyclophosphamide, doxorubicin, and 5-fluorouracil plus sequential medroxyprogesterone acetate alternating with tamoxifen) was 14 months compared to chemotherapy only arm (cyclophosphamide, doxorubicin, and 5-fluorouracil) where the survival was only 11 months ($p > 0.05$) [32].

14.11 Future Research

The future of management of recurrent endometrial cancer is likely to lie in precision medicine. Up till now the incorporation of genomic or proteomic profiling for individual patient tumors is not done routinely in clinical practice. Selection of patient is based on hormone receptor expression. With the advent of molecularly enhanced hormone therapy, hormone receptor expression can be boosted even in tumors devoid of hormone receptor expression [2].

To summarize, the treatment of recurrent endometrial cancer should be individualized with evidence of genetic and pathological background.

14.12 Key Points

- The overall rate of recurrence for endometrial cancer is approximately 10–15%; Over 50% of cases occur within 2 years of primary treatment.
- The outcome of REC mainly depends on the site of recurrence, tumor grade and histology, disease-free interval, and prior treatment.
- The therapeutic options available for REC are surgery, chemotherapy, radiotherapy, hormonal, and targeted therapy; a combination of the various modalities may also be given.
- Surgery is successful in the treatment of REC in women who have isolated recurrence in previously irradiated pelvis; Exenterative and non-exenterative procedures can be done to achieve complete cytoreduction.
- Radiation is most appropriate in women with local pelvic recurrence and no prior history of radiation therapy (5-year OS-53–75%).
- Role of chemotherapy in REC is mainly palliative and first-line therapy is Platinum-based therapy (either TP or TAP).
- Hormonal therapy gives best results in women with REC who have positive ER/PR status with low-grade disease. Both progestin and antiestrogen regimens have been tried with varying success.
- Targeted therapy in the form of VEGFR inhibitors or mTOR inhibitors is a new addition to the armamentarium for managing REC.

References

1. Aalders JG, Abeler V, Kolstad P. Recurrent adenocarcinoma of the endometrium: a clinical and histopathological study of 379 patients. Gynecol Oncol. 1984;17:85–103.
2. Bradford LS, Rauh-Hain JA, Schorge J, Birrer MJ, Dizon DS. Advances in the management of recurrent endometrial cancer. Am J Clin Oncol. 2015;38(2):206–12.
3. 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.
4. Carlson MJ, Thiel KW, Leslie KK. Past, present and future of hormonal therapy in recurrent endometrial cancer. Int J Womens Health. 2014;6:429–35.
5. Del Carmen MG, Boruta DM, Schorge JO. Recurrent endometrial cancer. Clin Obstet Gynecol. 2011;54:266.
6. Koh WJ, Abu-Rustum NR, Bean S, et al. Uterine neoplasms, version 1.2018, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2018;16(2):170–99.
7. Rauh-Hain JA, Del Carmen MG. Treatment for advanced and recurrent endometrial carcinoma combined modalities. Oncologist. 2010;15(8):852–61.
8. Morgan JD 3rd, Reddy S, Sarin P, et al. Isolated vaginal recurrences of endometrial carcinoma. Radiology. 1993;189:609–13.
9. Hoekstra CJ, Koper PC, Van Putten WL. Recurrent endometrial adenocarcinoma after surgery alone: prognostic factors and treatment. Rad Oncol. 1993;27:164–6.
10. McMeekin DS, Filiaci VL, Thigpen JT, 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;106:16.
11. Morice P, Leary A, Creutzberg C, Abu-Rustum N, Darai E. Endometrial cancer. Lancet. 2016;387(10023):1094–108.
12. Nout RA, Van de Poll-Franse LV, Lybeert ML, 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.
13. Papadia A, Bellati F, Ditto A, et al. Surgical treatment of recurrent endometrial cancer: time for a paradigm shift. Ann Surg Oncol. 2015;22(13):4204.
14. Bristow RE, Santillan A, Zahurak ML, et al. Salvage cytoreductive surgery for recurrent endometrial cancer. Gynecol Oncol. 2006;103:281–7.
15. Schmidt AM, Imesch P, Fink D, Egger H. Pelvic exenteration for advanced and recurrent endometrial cancer: clinical outcomes of 40 patients. Int J Gynecol Can. 2016;26:716–21.
16. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: results from a randomized trial. Gynecol Oncol. 2003;89:201.
17. Huh WK, Straughn JM Jr, Mariani A, et al. Salvage of isolated vaginal recurrences in women with surgical stage I endometrial cancer: a multi-institutional experience. Inter J Gynecol Can. 2007;17:886.
18. Viswanathan AN, Cormack R, Holloway CL, et al. Magnetic resonance-guided interstitial therapy for vaginal recurrence of endometrial cancer. Int J Rad Oncol Biol Phys. 2006;66:91.
19. 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(19):3902–8.
20. Aapro MS, Van Wijk FH, Bolis G, et al. European Organisation for Research and Treatment of Cancer Gynaecological Cancer Group. Doxorubicin versus doxorubicin and cisplatin in endometrial carcinoma: definitive results of a randomised study (55872) by the EORTC Gynaecological Cancer Group. Ann Oncol. 2003;14(3):441–8.
21. 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(11):2159–66.

22. 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.
23. Miller D, Filiaci V, Fleming G, et al. Randomized phase Ill non-inferiority trial of first line chemotherapy for metastatic or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. Int Gynecol Oncol. 2012;125(3):771.
24. 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):796–805.
25. 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(6):1736.
26. Colombo N, Creutzberg C, Amant F, et al. ESMO–ESGO–ESTRO consensus conference on endometrial cancer: diagnosis, treatment and follow-up. Radiol Oncol. 2015;117(3):559–81.
27. 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(6):1736–44.
28. Whitney CW, Brunetto VL, Zaino RJ, et al. Phase II study of medroxyprogesterone acetate plus tamoxifen in advanced endometrial carcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92(1):4–9.
29. Thigpen T, Brady MF, Homesley HD, Soper JT, Bell J. Tamoxifen in the treatment of advanced or recurrent endometrial carcinoma: a Gynecologic Oncology Group study. J Clin Oncol. 2001;19(2):364–7.
30. Scarabelli C, Campagnutta E, Giorda G. Maximal cytoreductive surgery as a reasonable therapeutic alternative for recurrent endometrial carcinoma. Gynecol Oncol. 1998;70:90–3.
31. Makker V, Green AK, Wenham RM, Mutch D, Davidson B, Miller DS. New therapies for advanced, recurrent, and metastatic endometrial cancers. Gynecol Oncol Res Pract. 2017;4(1):19.
32. Thigpen JT, Blessing J, Disaia P. Oral medroxy progesterone 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, Parthenon; 1986. p. 446–7.

Non-Endometrioid Histologies: What Is New?

15

Monisha Gupta

Worldwide, endometrial cancer (EC), also known as corpus uteri cancer, is the sixth most common cancer among women. In India, it is the tenth most common cancer accounting for 2.3% of all cancers among women. According to GLOBOCAN 2018, there were 13,328 new cases of endometrial cancer and EC was responsible for an estimated 5010 cancer deaths [1].

Based upon histopathological features, ECs are commonly categorized as Endometrioid (Type I) and Non-Endometrioid (Type II) cancers that include Uterine papillary Serous carcinoma (UPSC), Carcinosarcoma, Clear cell carcinoma (CCC), and less commonly mixed histologies (Table 15.1). In general, Type I ECs accounts for majority of cases (70–80%) and are associated with favorable prognosis [2]. On the other hand, Type II ECs accounts for 40% of EC-related deaths due to their aggressive biological behavior, intrinsic chemoresistance, and advanced stage at presentation [2, 3].

15.1 Distinct Molecular Variations Between Endometrioid and Non-Endometrioid EC

Recently, by wide genomic analysis of more than 350 women with EC, the Cancer Genomic Atlas (TCGA) research network categorized ECs in subgroups based upon molecular characteristics: significant microsatellite instability (MSI), few copy number variations, mutations in POLE (a subunit of DNA Polymerase Epsilon) and increased activation of WNT/CTNNB1 pathway for Type I ECs [4].

Also, within type II cancers, distinct histological subtypes show unique molecular signatures [5, 6]. Correct genomic classification of the tumor can help to form more objective diagnosis of tumor type, consequently leading to right therapy. For

M. Gupta (✉)
Department of Gynecology Oncology, Max Institute of Cancer Care, Shalimar Bagh, Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_15

Table 15.1 Epidemiological, clinical, and molecular alterations between type I and type II tumors

	Type I	Type II
Incidence	>80%	<20%
Age	Varied	Postmenopause
Histology	Endometrioid	Serous, clear cell, carcinosarcoma, mixed histologies
Grade	Low	High
Clinical behavior	Less aggressive	More aggressive
Estrogen relation	More evidence	Less evidence
BMI	High	Low
Precursor lesion	EIN, hyperplasia with or without atypia	EIN, uncertain
IHC	50–80% PTEN mutation 14–20% p53 mutation 10–20% E-cadherin 20–45% MSI 14–44% b-catenin 10–18% aneuploidy 10–30% K-ras mutation Often with ER, PR, or AR positivity	0–5% PTEN mutation 90% p53 mutation 80–90% E-cadherin 0% MSI 0–5% b-catenin 85–95% aneuploidy 45–80% Her/neu overexpression P16 mutation

Example, Type II ECs are almost always treated with adjuvant therapy, even though they show low response rates. Thus, there is a need to build new predictive biomarkers in particular for women with Type II ECs.

Table 15.1 gives an overview of the frequency of mutations in Type I and II EC.

Various targeted therapies in EC.

The improved knowledge about the molecular profile of EC should ideally be translated into more personalized targeted therapy and improved survival outcome. However, so far, the only FDA approved targeted therapy for ECs is hormonal intervention and the immune checkpoint inhibitor, pembrolizumab. Specifically, for Type II ECs, there are no approved targeted therapies.

1. An overview of molecular profile associated potential treatment options has been illustrated in Table 15.2.
2. Molecular analysis has revealed PI3K pathway to be the most commonly mutated pathway for the ECs. Thus, targeted therapies via multiple kinase inhibitors have been evaluated. Weigett et al. in their study have shown that EC cell lines with mutations in the PI3K pathway are more sensitive to PI3K and mToR inhibitors while KRAS mutant ECs did not respond to mToRC1 treatment in clinical phase II trials [7].

   A genomic analysis by Kuhn et al. demonstrated that PIK3CA was mutated/amplified in 48% of uterine papillary serous cancer (UPSC) women, thus, mToR inhibitors such as rapamycin might be used in the adjuvant treatment of UPSC women [8].

Table 15.2 Histologic-specific molecular profile summary and associated potential treatment options

Histology	Molecular alterations	Treatment implications
Serous	Highest Her2 expression/ amplification Highest AR expression, high ER/ PR Highest TP53 mutation	HER2-directed therapy Hormonal therapy and anti-androgens Wnt-directed inhibitor Platinum sensitivity
Carcinosarcoma	Highest PD-1 and High PD-L1 expression High BRCA1/2 mutation High TP53 mutation	PD1/PDL-1-directed immunotherapy Platinum and PARP inhibitors Wnt-directed inhibitor
Clear cell carcinoma	High Her2 expression/ amplification High C-Met expression Highest ERBB2 mutation Highest BRCA1 mutation	HER2-directed therapy C-Met inhibitors Tyrosine kinase receptor inhibitors PARP inhibitor
Endometrioid adenocarcinoma	Highest ER/PR Highest PI3KCA mutation High PD-L1 High BRCA2 mutation	Hormone therapy and anti-estrogens PTEN loss PI3K inhibitors PD1/PDL-1-directed immunotherapy Platinum and PARP inhibitors

3. Furthermore, in Type II ECs, pharmacological targeting of Her-2 has also gained interest as a potential therapeutic strategy. Study has revealed that dual inhibition with trastuzumab (anti-Her-2 antibody) and lapatinib (small molecule TKI) in serous EC xenograft showed significant antitumor activity. However, this effect was only observed in the Her-2 amplified serous EC cell line, again emphasizing the importance of molecular classification over histological categorization of ECs [9].

   According to a randomized phase II study of carboplatin, paclitaxel with or without trastuzumab for advanced or recurrent UPSC women with 3 + IHC for Her-2/neu [10], addition of trastuzumab to carboplatin–paclitaxel was well tolerated and led to increased progression-free survival.
4. Mutations in PPP2RIA'S phosphatase-2 are reported in as high as 32% of UPSC and is located downstream of Her 2/neu, which may be found as a potential target for treatment of UPSC. Also, it was found that the same mutations were infrequent in endometrioid cancer and absent in clear cell and carcinosarcoma subtypes [11].

15.2 Uterine Papillary Serous Carcinoma

By definition, all uterine serous carcinoma are high grade. UPSC exhibit papillary architecture very similar to serous ovarian carcinomas. Approximately, 70% of women will present with extrauterine disease. They account for only 8–10% of all ECs, but are responsible for 40% of EC-related deaths.

In UPSC, if the serous counterpart of tumor is greater than 10%, but less than 90%, the tumor is considered as mixed serous histology. In a review study, the pure UPSC group had an almost threefold risk of recurrence and death as compared to mixed cell histology [12].

15.2.1 Surgical Management

Surgical staging is the first line of treatment for majority of ECs. This includes total abdominal hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and para-aortic lymph node dissection as per FIGO 2019 Guidelines. Unlike Type I ECs, where the therapeutic value of complete lymphadenectomy is still debatable; in Type II ECs, complete pelvic and para-aortic lymphadenectomy has been shown to improve survival for the patient [13]. For early-stage I and II UPSC, lymphadenectomy helps to tailor postoperative adjuvant therapy.

15.2.2 Adjuvant Management

With observation alone, the recurrence rate for women with UPSC with no myometrial invasion in early-stage ranges from 0–30%. However, it drastically increases from 30% to 80% with myometrial invasion [14].

As per GOG 209, standard adjuvant therapy for UPSC patient is chemotherapy with Paclitaxel and carboplatin with or without vaginal brachytherapy. In a phase II trial by Fields et al. [15], sandwich therapy that includes three cycles of carboplatin and Paclitaxel followed by whole abdominal radiation (WAR) and subsequent, three more cycles of chemotherapy have demonstrated 75% survival rates in women with early serous carcinoma. According to another study by Fader et al. [16], the recurrence rate for early-stage UPSC women is 8.7% with chemotherapy as compared to 25% with radiation alone.

Thus, according to 2009 Society of Gynaecologic Oncology (SGO) Consensus, chemotherapy with or without radiation for early-stage UPSC has been recommended.

15.3 Carcinosarcoma

Uterine carcinosarcoma (UCS) also called as malignant mixed Mullerian tumors (MMTs) are currently considered as a variant of endometrial adenocarcinoma due to their similar risk factors, epidemiology and clinical behavior including pattern of spread. UCS is an uncommon but aggressive histology with a poor median survival for the patient.

UCS contains both carcinomatous (epithelial) and sarcomatous (connective tissue) elements and depending upon the type of connective tissue, they are further divided into homologous and heterologous variety. However, the epithelial component has been suggested to be more aggressive as both local and distant metastasis shows only epithelial components. Studies have shown that 6%, 31%, and 75% of all UCSs are associated with mutations in KRAS, PIK3CA, and TP53, respectively [17].

The median age at presentation in UCS is 62–67 years and about 60% of women will have disease outside the uterus. A preoperative evaluation with CA-125 is recommended as it correlates with tumor stage and myometrial invasion of more than half at a cut off value of 30 U/ml [18].

The "conversion theory "is the most accepted theory for the development of UCS, where the mesenchymal component is thought to arise from carcinomatous elements through metaplastic transformation. This takes place through epithelial–mesenchymal transition (EMT) where a polarized epithelial cell assumes mesenchymal phenotype and thus, gets the ability to migrate away from the original epithelial layer. The fact that different histological components of most UCSs show common chromosomal abnormalities well supports the EMT theory [19].

15.3.1 Management

Uterine carcinosarcoma has the same FIGO staging as for endometrial adenocarcinoma. The primary treatment for UCS shall depend upon the extent of tumor spread.

For uterus and pelvis confined disease or metastatic disease limited to abdomen, the initial line of management will be surgical resection. This will include total abdominal hysterectomy, bilateral salpingo-oophorectomy, bilateral pelvic and para-aortic lymph node dissection, omentectomy, and removal of all gross abdominal disease. Studies have recommended complete pelvis and para-aortic lymph node dissection for all UCSs as it impacts stage (thus, prognosis for the patient) and improves overall survival [20].

Minimal invasive approach has been considered safe for stage I and II UCS regarding survival outcomes and risk of recurrence compared to open approach [21].

For women with extra-abdominal spread, primary surgical resection has a limited value, and intent of treatment should be palliative, however complete cytoreduction improves prognosis and survival outcomes.

For women who have undergone incomplete surgery initially (when the diagnosis of UCS had been made upon postoperative review of surgical specimen), a

second surgery to complete the surgical staging, including lymph node dissection, is usually warranted.

15.3.2 Adjuvant Therapy

Currently, there is insufficient data regarding whether adjuvant treatment improves survival outcomes in stage IA women, thus, these women can be offered adjuvant therapy or can be kept on observation [22].

Adjuvant therapy is definitely indicated in stage IB-IV stage UCS as it has been shown to improve overall survival. Cochrane has reviewed 3 randomized trials comprising 579 women with UCS, evaluating radiation therapy and/or systemic therapy for stage III/IV UCS. Two trials have shown superiority of combination chemotherapy over ifosfamide alone (with significantly lower risk of disease progression and death in combination arm) in women with stage III/IV persistent or recurrent disease. However, one trial found no difference in disease progression and death in women treated with whole abdominal radiation (WAR) and chemotherapy. Thus, Cochrane concluded two recommendations [23, 24]:

1. Radiation therapy to abdomen is not associated with improved survival.
2. For advanced-stage metastatic and recurrent disease, combination chemotherapy with ifosfamide and paclitaxel should be the adjuvant treatment. Due to toxicities associated with ifosfamide, carboplatin can be given instead.

15.3.3 Prognosis

Overall, as compared to high-risk endometrial carcinoma, UCS has a poor prognosis. The most important prognostic factor for women with UCS is surgical stage. Regardless of therapy, the 5-year disease-specific survival rates are 59% for stage I/II disease, 225 for stage III, and only 9% for stage IV disease [25, 26]. Even in the early stage, studies have shown that a heterologous sarcomatous component is a strong negative prognostic factor with a 3-year overall survival rate of 45% in women with heterologous versus 93% with homologous components [25].

Other factors associated with worse prognosis in women with UCS include depth of myometrial invasion, presence of lympho-vascular space involvement, lymph node metastasis, and presence of peritoneal disease [21, 26].

Studies have evaluated the role of complete cytoreductive surgery (CRS) in women with UCS. Absence of any residual disease at the end of CRS is associated with better overall survival (OS) in stage III and IV disease [26, 27]. Similarly, complete lymphadenectomy has shown to improve prognosis in women with UCS. According to retrospective SEER data, the 5-year OS increase from 33.4 to 35.8% and there was a 6-month benefit in median OS (from 23 to 29 months) in women with stage I–II UCS after lymphadenectomy [27].

15.4 Clear Cell Carcinoma

Uterine clear cell carcinoma (UCCC) is an uncommon type II histology, accounting for less than 5% of all endometrial cancers. The median age at presentation is 66 to 68 years in postmenopausal women. Despite being a high-risk disease, UCCC are usually confined to uterus (stage I–II), with myometrial invasion in more than 50% women and LVI in 25–40% women. Lymph node involvement has been found to be more frequent for Type II tumors including clear cell carcinoma of uterus [28].

Limited information is available in literature about biological characteristics and precursor lesions of UCCC. In contrast to their cervical and vaginal counterparts, no association with diethylstilbestrol has been described for UCCC. Some studies [29] have observed a spectrum of nonspecific atypical glandular changes in the endometrium adjacent to clear cell carcinoma with a frequency of 90% out of 30 cases and 0% of 68 controls represented by either benign or endometrioid carcinoma. Thus, they concluded that these lesions could be the precursor lesions for UCCC.

Clear cell Carcinoma exhibit a classical immune-histochemistry profile, including all sites: positivity for CK 7, CAM 5.2, CEA, Vimentin, p-53, and CA-125; negativity for CK 20 and PR and variable positivity for ER and HER-2/neu. Studies have correlated P53 overexpression more for UCCC as compared to endometrioid adenocarcinoma but less frequently than UPSC [30].

15.4.1 Management

As for all endometrial cancers, the standard surgical management for UCCC consists of total abdominal hysterectomy, bilateral salpingo-oophorectomy, and extensive surgical staging (including omentectomy, bilateral pelvic, and para-aortic lymph node dissection and peritoneal washings). In a study by Cirisano et al. [31], in women with clinical stage I–II endometrial cancer, it was shown that upstaging to stage III–IV occurred in 30% of UCCC, 47% with UPSC and only 12% in women with endometrioid adenocarcinoma, thus, emphasizing the need of extensive surgical staging for type II ECs.

Also, in a study by Thomas et al. [32], 52% of women with clinical stage I–II UCCC were found to have extrauterine disease during comprehensive surgical staging. In the same study, women with stage IIIC to IV disease who were completely cytoreduced to no residual disease had a superior PFS and OS compared with women with residual disease at the end of surgery.

15.4.2 Adjuvant Management

The optimal postoperative adjuvant management for UCCC is difficult to define as only a small number of women get affected by UCCC, thus making it difficult to discern the factors associated with improved outcome in UCCC. Moreover,

majority of studies have included women with UCCC along with UPSC, thus, making it difficult to know the pattern of failure exclusively for UCCC.

In 2009, SGO recommended the use of adjuvant chemotherapy with cisplatin, taxol, and doxorubicin for women with stage III–IV disease and recurrent disease. Also, SGO has stated that adjuvant pelvic radiation and/or WAR has not been beneficial in women diagnosed with UCCC. However, they have also recommended that due to relatively high incidence of distant recurrences in UCCC, use of adjuvant platinum-based chemotherapy may be reasonable with stage I and II UCCC after proper counselling.

15.4.3 Prognosis

Clear cell carcinoma of uterus carries a worse prognosis as compared to endometrioid adenocarcinoma [28]. In the study by McMeekin et al. [33], the hazard ratio (HR) for progression and death in women with UCCC was 1.52 and 1.51, respectively compared with those with other histological subtypes. Some studies have shown better survival outcomes for early-stage UCCC as compared to stage-matched UPSC. For instance, Carcangiu et al. [34] have compared 5-year survival for stage I UCCC versus UPSC (72% vs 44%) and corresponding 5-year survival rates for stage II disease were 59% and 32%, respectively.

Several studies have evaluated various clinicopathological factors associated with survival in UCCC. In a Norwegian study including 181 women with UCCC [28], age, LVSI, clinical and pathological stage, and myometrial invasion were significantly related to survival. On the other hand, Murphy et al. [35] found no corelation between recurrence rate and tumor stage, myometrial invasion, peritoneal cytology, and involvement of extrauterine sites. Similarly, Carcangiu also found no corelation between myometrial invasion, LVSI, and survival of women with stage I–II UCCC.

In a study by Lee et al. [36], UCCC has been shown to be associated with high risk of venous thromboembolism (VTE) (34.5% in UCCC versus 13.8% for high-grade endometrioid adenocarcinoma) and among women with UCCC, VTE has an adverse effect on survival (HR = 3.65).

15.5 Conclusions

Endometrial carcinomas were traditionally classified as the histologically low-grade type I tumors and high-grade type II tumors. Type II (non-endometrioid) carcinomas have a very aggressive behavior and different molecular profile as compared to type I carcinomas. For optimal management, complete staging with pelvic and paraaortic lymph node dissection and omentectomy followed by chemoradiation is recommended for improved survival in early stages. For advanced stage, complete cytoreduction with no residual disease followed by chemotherapy has been shown to improve survival.

Key Points

1. Endometrial carcinomas are broadly divided in to type I and type II based on different molecular alterations.
2. Majority of type I tumors show alterations in MSI (microsatellite instability) and exhibit mutations in PTEN, KRAS, PIK3CA, and CTNNB1.
3. Type II cancers show P53 alterations, LOH (loss of heterozygosity) on several chromosomes, as well as molecular alterations affecting p16, E-cadherin, and c-erb-B2.
4. TGCA has reclassified endometrial carcinomas into four groups based on molecular characteristics, with the POLE-mutated group having very good survival.
5. Better understanding about molecular profile of ECs, including type II tumors leads to better management and thus, improved survival for ECs. Therefore, several studies are evaluating various targeted therapies (specifically for type II tumors) during adjuvant treatment.
6. Uterine papillary serous cancer (UPSC) is an aggressive subtype of type II tumors. Pure UPSC group carries worse survival outcomes as compared to mixed groups. Complete cytoreduction with no residual disease is warranted for all cases of UPSC. According to SGO 2009 consensus, chemotherapy with or without radiation is recommended for early-stage UPSC.
7. Uterine carcinosarcoma (UCS) is another aggressive histology, associated with poor outcomes. The conversion theory through epithelial–mesenchymal transition is the most accepted theory for origin of carcinosarcoma. Complete cytoreduction has been shown to improve survival in many studies. Adjuvant chemotherapy with radiotherapy is recommenedd in advanced stages. Among prognostic variables, the surgical stage is the most important prognostic variable associated with survival.
8. Uterine clear cell cancer (CCC) is an uncommon subtype of type II tumors. Literature is scarce about biological features and precursor lesions of UCCC. They exhibit a classical immunohistochemistry profile. Complete surgical staging is warranted for all cases of UCCC as disease may be upstaged in 30–40% cases. In 2009, SGO recommended adjuvant chemotherapy for all advanced stage and recurrent UCCC. UCCC has a poor survival outcome as compared to endometrial adenocarcinoma and is associated with a high risk of venous thromboembolism.

References

1. Cancerindia.org.in>globocan 2018-india-factsheet.
2. Liu F-S. Molecular carcinogenesis of endometrial cancer. Taiwan J Obstet Gynecol. 2007;46(1):26–32.
3. 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.
4. Kandoth C, Schultz N, Cherniack AD, et al. Integrated genomic characterization of endometrial carcinoma. Nature. 2013;497:67–73.
5. Jones NL, Xiu J, Reddy SK, et al. Identification of potential therapeutic targets by molecular profiling of 628 cases of uterine serous carcinoma. Gynecol Oncol. 2015;138:620–6.

6. Lax SF, Kendall B, Tashiro H, et al. 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;88:814–24.
7. Weigelt B, Warne PH, Lambros MB, et al. PI3K pathway dependencies in endometrioid endometrial cancer cell lines. Clin Cancer Res. 2013;19(13):3533–44.
8. Kuhn E, Wu RC, Guan B, et al. Identification of molecular pathway aberrations in uterine serous carcinoma by genome-wide analyses. J Natl Cancer Inst. 2012;104(19):1503–13.
9. Aertgeerts K, Skene R, Yano J, et al. Structural analysis of the mechanism of inhibition and allosteric activation of the kinase domain of HER2. J Biol Chem. 2011;286:18756–65.
10. Amanda NF, Dana MR, Eric S, et al. Randomized phase II trial of carboplatin-paclitaxel versus carboplatin-paclitaxel-trastuzumab in uterine serous carcinomas that overexpress human epidermal growth factor receptor 2/neu. J Clin Oncol. 2018;36(20):2044–51.
11. Nagendra DC, Burke J, Maxwell GL. PPP2R1A mutations are common in the serous type of endometrial cancer. Mol Carcinog. 2012;51(10):826–31.
12. Roelofsen T, Wiersma VH, van Tilburg JM, et al. Pure compared with mixed serous endometrial carcinoma: two different entities? Obstet Gynecol. 2012;120:1371.
13. Todo Y, Kato H, Kaneuchi M, et al. Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. Lancet. 2010;375(9721):1165–72.
14. Fader AN, Boruta DM, Olawaiye AB, et al. Uterine papillary serous cancer: epidemiology, pathogenesis and management. Curr Opin Obstet Gynecol. 2012;22:21–9.
15. Fields AL, Einstein MH, Novetsky AP, 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;108:210–6.
16. Fader A, Santin AD, Gehrig PA, et al. Early stage uterine serous carcinoma: management updates and genomic advances. Gynecol Oncol. 2013;129:244–50.
17. McConechy MK, Ding J, Cheang MC, et al. Use of mutation profiles to refine the classification of endometrial carcinomas. J Pathol. 2012;228:20–30.
18. Dave KS, Chauhan A, Bhansali R, et al. Uterine Carcinosarcomas: 8-year single centre experience of 25 cases. Indian J Med Paediatr Oncol. 2011;32:149.
19. Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. J Clin Invest. 2009;119(6):1420–8.
20. Park JY, et al. The role of pelvic and/or para-aortic lymphadenectomy in surgical management of apparently early carcinosarcoma of uterus. Ann Surg Oncol. 2010;17(13):861–8.
21. Fader AN, et al. Impact of histology and surgical approach on surviving among women with early-stage, high-grade uterine cancer: an NRG oncology/gynecologic oncology group ancillary analysis. Gynecol Oncol. 2016;143(3):460–5.
22. Cantrell LA, Havrilesky L, Moore DT, et al. A multi-institutional cohort study of adjuvant therapy in stage I-II uterine Carcinosarcoma. Gynecol Oncol. 2011;127:22.
23. Galaal K, et al. Adjuvant radiotherapy and/or chemotherapy after surgery for uterine Carcinosarcoma. Cochrane Database Syst Rev. 2013;2:CD006812.
24. Galaal K, et al. Adjuvant radiotherapy and/or chemotherapy after surgery for uterine Carcinosarcoma. Cochrane Database Syst Rev. 2011;1:CD006812.
25. Gonzalez Bosquet J, et al. The impact of multi-model therapy on survival for uterine carcinosarcomas. Gynecol Oncol. 2010;116(3):419–23.
26. Yamada SD, et al. Pathological 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.
27. Alagkiozidis I, et al. Survival impact of cytoreduction to microscopic disease for advanced stage cancer of the uterine corpus a retrospective cohort study. Int J Surg. 2015;14:61–6.
28. Abeler VM, Vergote IB, Trope CG. Clear cell carcinoma of endometrium. Prognosis and metastatic pattern. Cancer. 1996;78:1740–7.
29. Fadare O, Liang SX, Ulukus EC, et al. Precursors of endometrial clear cell carcinoma. Am J Surg Pathol. 2006;30:1519–30.

30. Vang R, Whitaker BP, Farhood AI, et al. Immunohistochemical analysis of clear cell carcinoma of the gynaecological tract. Int J Gynecol Pathol. 2001;20:252–9.
31. Cirisano FD, Robboy SJ, Dodge RK, et al. Epidemiological and surgico-pathological findings of papillary serous and clear cell endometrial cancers when compared to endometrioid carcinoma. Gynecol Oncol. 1999;74:385–94.
32. Thomas M, Mariani A, Wright JD. Surgical management and adjuvant therapy for patients with uterine clear cell carcinoma: a multi-institutional review. Gynecol Oncol. 2008 Feb;108(2):293–7.
33. McMeekin DS, Filiaci VL, Thigpen JT, et al. Gynecologic oncology group study: the relationship between histology and outcome in advanced and recurrent endometrial cancer patients participating in first-line chemotherapy trials. Gynecol Oncol. 2007;106:16–22.
34. Carcangiu ML, Chambers JT. Early pathological stage clear cell carcinoma and uterine papillary serous carcinoma of the endometrium: comparison of clinic-pathological features and survival. Int J Gynecol Pathol. 1995;14:30–8.
35. Murphy KT, Rotmensch J, Yamada SD, et al. Outcome and pattern of failure in pathological stage 1-1V clear cell carcinoma of endometrium: implications of adjuvant radiation therapy. Int J Radiat Oncol Biol Phys. 2003;55:1272–6.
36. Lee L, Garrett L, Lee H, et al. Association of clear cell carcinoma of the endometrium with a high rate of venous thromboembolism. J Reprod Med. 2009;54:133–8.

Part IV

Other Uterine Cancers

Uterine Sarcomas: Review and Update

16

Kanika Batra Modi

16.1 Introduction

Uterine sarcomas, fall under the broad category of soft tissue sarcomas, which are extremely rare regardless of the site of origin and account for 3–9% of uterine malignancies [1]. Uterine sarcomas (US) arise from dividing cell populations in the myometrium or connective tissue elements within the endometrium. Compared with the more common endometrial carcinomas (epithelial neoplasms), uterine sarcomas, particularly leiomyosarcomas, behave aggressively and are associated with a poorer prognosis. The pathogenesis of uterine sarcoma remains largely unknown, although recent basic science and preclinical animal models have provided a better understanding of tumor biology.

Although the prevalence of these tumors is very low, they still generate a stir of interest because of their poor prognosis and high mortality rates due to the aggressiveness of the disease.

16.2 Classification

World Health Organization and the College of American Pathologists have published classification systems for uterine sarcomas. Uterine sarcomas can be broadly classified into [2]:

a. Leiomyosarcomas (uLMS).
b. Endometrial Stromal Sarcoma (ESS).
c. Undifferentiated Uterine Sarcoma (UUS).
d. Rare subtypes include adenosarcoma, rhabdomyosarcoma, and perivascular epitheilioid cell neoplasm (PEComa).

K. Batra Modi (✉)
Max Institute of Cancer Care, Max Hospital, Saket, New Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_16

Historically, uterine carcinosarcoma was classified as a type of uterine sarcoma and was termed malignant mixed Müllerian tumor or mixed mesodermal sarcoma. However, these neoplasms are now reclassified as carcinomas since they are derived from monoclonal neoplastic cell, which has more characteristics of epithelial than stromal neoplasms. In addition, the epidemiology, risk factors, and clinical behavior associated with carcinosarcoma suggest a closer relationship to endometrial carcinoma than to sarcoma. Hence, carcinosarcoma are now classified as mixed epithelial and Mullerian tumors [3].

16.3 Epidemiology and Risk Factors

Of all the histological subtypes, leiomyosarcomas are the most common type, constituting about two-thirds of all cases. Endometrial stromal sarcomas (ESS) are about 25% of all uterine sarcomas while the other types are rare [4]. ESS are typically low-grade tumors and the undifferentiated subtype (previously called high-grade ESS) is a separate entity now. The median onset of uterine sarcomas is 50–70 years depending on the histological subtypes, but most women are of postmenopausal age [5]. In a SEER data analysis, at the time of diagnosis, 18.6% of patients were aged 30–49 years, 49.8% were aged 50–69 years, and 31.6% were aged 70 years or older [6].

Black women have a higher overall incidence and poorer prognosis of all types of uterine sarcoma in comparison to white women. The age-adjusted incidences of leiomyosarcomas for black and white women, respectively, were 1.5 and 0.9 per 100,000 in the SEER analysis [6]. The overall age-adjusted incidence rate for black women was twice that of white women and more than twice that of women of other races (7.3/105 vs 3.5/105 vs 3/105, $P > 0.0001$) [6].

Prior history of radiation has been associated with an increased risk of uterine sarcomas [7]. Use of tamoxifen for breast cancer may be associated with increased risk of uterine sarcomas. In a study by Lavie et al. [8], who analyzed 1507 cases of women with breast cancer, found an incidence of 1.9% among those who received tamoxifen versus an incidence of 0.6% among those who did not receive tamoxifen (Odd's Ratio 3.1, CI 1–9.1). A substantial increase in incidence has been seen with at least 4 years of tamoxifen use (OR, 6.6; CI 2.0–22.1) [8].

Recently, the Finnish Cancer Registry revealed an increased association between estradiol–progestin use and increased risk of uterine sarcomas (for leiomyosarcoma standardized incidence ratio, 1.6 and for ESS 1.4) [9]. However, Schwartz et al. had reported a statistically non-significant but positive correlation between oral contraceptive use and sarcoma risk [10]. Given the very low overall incidence of these cancers, use of hormones is not curbed in general population.

A hereditary predisposition of uterine sarcomas appears to be associated with certain syndromes like Hereditary nonpolyposis colorectal cancer (HNPCC) [11], and hereditary retinoblastoma [12]. Hysterectomy for prophylaxis is recommended

for women with HNPCC, once the family is completed, due to the high risk of endometrial cancer and hence may safeguard against sarcomas.

Other risk factors like high body mass index, diabetes and smoking do not have a proven association with uterine sarcomas [13].

16.4 Staging

FIGO 2009 staging for leiomyosarcoma and endometrial stromal sarcoma (Table 16.1) and adenosarcoma (Table 16.2) is given below.

Table 16.1 2009-revised FIGO and AJCC (TNM) staging system for leiomyosarcomas and endometrial stromal sarcoma

Stage		Definition
I		Tumor limited to uterus
	IA	≤5 cm
	IB	>5 cm
II		Tumor extends beyond the uterus, within the pelvis
	IIA	Adnexal involvement
	IIB	Involvement of other pelvic tissues
III		Tumor invades abdominal tissues (not just protruding into the abdomen)
	IIIA	One site
	IIIB	>one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis

Table 16.2 2009-revised FIGO and AJCC (TNM) staging system for adenosarcoma

I		Tumor limited to uterus
	IA	Tumor limited to endometrium/endocervix with no myometrial invasion
	IB	Less than or equal to half myometrial invasion
	IC	More than half myometrial invasion
II		Tumor extends beyond the uterus, within the pelvis
	IIA	Adnexal involvement
	IIB	Involvement of other pelvic tissues
III		Tumor invades abdominal tissues (not just protruding into the abdomen)
	IIIA	One site
	IIIB	>one site
	IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
IV	IVA	Tumor invades bladder and/or rectum
	IVB	Distant metastasis

16.5 Leiomyosarcoma

Leiomyosarcomas are malignant smooth muscle tumors, which typically arise de novo mostly, but a small percentage is also suggested to be a conversion of benign leiomyomas to malignant ones. They are typically solitary, tan masses on gross section, which are poorly circumscribed and can have variable hemorrhagic and necrotic areas in between.

Microscopically, three important pathological criteria include cytological atypia, mitoses, and coagulative necrosis. There are two variants of leiomyosarcoma:

- Epithelioid leiomyosarcoma—They typically have round to polygonal cells rather than the typical spindle-shaped cells, with large amounts of eosinophilic or clear cytoplasm. The presence of atypia and $\geq$ 3 mitoses per 10 high power fields, with necrosis in 50% cases, can be classified as leiomyosarcoma of epithelioid type [14]. They are known to be more aggressive in nature and tend to metastasize [15].
- Myxoid leiomyosarcomas—They are less common and can be difficult to diagnose due to the lack of typical histopathological features of tumor cell necrosis, atypia, or mitosis. Due to the presence of myxoid features, they behave in an aggressive manner clinically [16].

The staging systems have a limited capacity for prognostication and a detailed molecular analysis helps to improve the understanding and prediction of various outcomes. Estrogen (ER) and progesterone (PR) receptor expression have been shown to have a positive correlation with disease prognosis in uterine leiomyosarcoma [17–19]. Cyclooxygenase-2 (COX-2) expression has been reported to have an independent poor prognostic marker in leiomyosarcoma patients [20]. High p53, p16, Ki67, and bcl-2 expression patterns help in the diagnosis of leiomyosarcomas. They are diagnosed by presence of smooth muscle markers, including desmin, h-caldesmon, histone deacetylase 8 (HDCA8), and smooth muscle actin.

16.5.1 Diagnosis

Clinically, they present with either abnormal uterine bleeding or pressure symptoms like lower abdominal pain and urinary frequency, or mass in lower abdomen. The diagnosis is difficult to make in clinical practice in premenopausal women and to differentiate it from fibroids. It can be typically suspected in women with presumed leiomyomas who have bleeding and pain out of proportion to the size of uterus. Rapidly growing uterine mass in postmenopausal women arises a strong suspicion of uterine sarcoma.

Pelvic ultrasound is usually the first investigation done in a suspected uterine pathology, which can show mixed echogenic and non-echogenic areas and central necrosis but they can be present in benign fibroids as well. The Morphological Uterus Sonographic Assessment group showed that uLMS often presents as purely

myometrial lesion and is typically a single, large tumor, resembling an ordinary myoma or it may appear as an irregularly vascularized mass, with a regular or irregular outline, often with irregular anechoic areas due to necrosis [21].

Regarding the choice of further imaging, there is little data to choose for as an investigation of choice and it is considered appropriate to order either magnetic resonance imaging (MRI), computed tomography (CT), or positron emission tomography (PET) with CT [22].

MRI due to its better soft tissue resolution is an appropriate tool in making a diagnosis and the findings suggestive of leiomyosarcoma are absence of calcifications, ill-defined margins intralesional hemorrhage [8–10]. Contrast-enhanced MRI (CE-MRI) has shown a significantly superior diagnostic accuracy and a significantly higher specificity than diffusion-weighted MRI (DW-MRI) in one of the studies; however, a combination of DW-MRI and apparent diffusion coefficient value of less than 1.08×10^{-3} mm^2/s can achieve a diagnostic accuracy comparable with CE-MRI [23].

Use of positron emission tomography/computed tomography (PET/CT) to differentiate between ordinary leiomyomas, leiomyoma variants, and LMS remains limited because ordinary leiomyomas can uptake ^{18}F-fluorodeoxyglucose in PET/CT [24].

Endometrial sampling can reveal a diagnosis of sarcoma but has a low sensitivity of about 62% [25]. A high serum LDH in fibroids can raise the suspicion of sarcoma and the PRE operative Sarcoma Score (PRESS) including age, serum LDH levels, endometrial cytological findings, and MRI findings were reported by Nagai et al. to have diagnostic accuracy, positive predictive value, negative predictive value, sensitivity, and specificity of 84%, 63%, 93%, 80%, and 85%, respectively [26].

16.5.2 Surgical Management

In early stages, with disease being confined to the uterus, a total hysterectomy is recommended. Women who have a preoperative suspicion of leiomyosarcoma, uterus should be removed en bloc, with maximal effort to avoid intraoperative rupture, morcellation, or spillage of tumor into the peritoneal cavity [27]. In perimenopausal and postmenopausal women, bilateral salpingo-oophorectomy is recommended, however, it is not known if it improves survival in premenopausal women and ovaries can be conserved in them. Ovarian metastasis is rare, with an incidence of just 3%, and occurs almost exclusively in cases with intraperitoneal spread [28].

Morcellator use is not recommended anymore in benign conditions of the uterus, especially after a safety alert ascertained by the US Food and Drug Administration (FDA) as there can be unexpected cancer whose prognosis will be worsened by its use [29]. If a postoperative diagnosis of leiomyosarcoma is made in women who underwent a surgery, a resurgery will be indicated if [14, 30]:

1. Ovaries are to be removed, especially in postmenopausal women.
2. Myomectomy or subtotal hysterectomy has been done.
3. Morcellation was done, to remove any residual peritoneal disease.

Lymphadenectomy can usually be omitted due to the low incidence of lymph node involvement. The latest guidelines say that if lymph node involvement is present (involvement is often already detected intraoperatively), then extrauterine or hematogenous metastasis is usually also present. This means that systematic pelvic and para-aortic lymphadenectomy is not associated with a better prognosis, and it is therefore generally not recommended and only bulky nodes should be removed [31].

For advanced cases, the role of surgery is controversial. For women with extension beyond the uterus but not invading the bladder or rectum, it can be managed with a complete cytoreduction with studies suggesting an improved survival [32, 33]. Cytoreduction should aim to achieve macroscopically complete resection in one specimen *enbloc* and minimize microscopically positive margins and lymphadenectomy may be warranted in this situation.

However, women who cannot be optimally cytoreduced surgically, doing surgery can be detrimental as it will be associated with a delay in the systemic management [34]. This is best achieved by resecting the tumor en bloc with adherent structures, even if not overtly infiltrated, because patients with no residual disease after surgical resection have an improved survival rate compared with those who undergo a suboptimal surgical resection [35].

16.5.3 Adjuvant Treatment

16.5.3.1 Early Stage

For cases with early-stage uterus-confined disease who have undergone resection with no tumor spillage, observation is the standard of care, as no adjuvant therapy either chemotherapy or radiation is helpful in improving survival. A randomized prospective trial conducted to understand if there is any benefit of the addition of chemotherapy in early-stage leiomyosarcoma after surgery failed to show any benefit in either progression-free survival (PFS), and overall survival (OS) in the chemotherapy arm [36]. Another EORTC randomized trial was conducted to understand the role of radiation therapy in early-stage (I and II) disease, which failed to show any benefit in either PFS or OS by addition of radiation therapy in these cases [37]. Postoperative RT did not improve local (20% with RT vs. 24% without RT) or distant progression rates.

16.5.3.2 Advanced Disease

In patients with advanced disease, stage III and IV who have undergone a complete cytoreduction of the tumor have a benefit in survival outcomes by addition of chemotherapy. Doxorubicin and ifosfamide are the most active agents investigated as primary single-agent chemotherapy in recurrent and advanced uterine leiomyosarcomas. Docetaxel and gemcitabine, followed by doxorubicin, or doxorubicin alone have been tried in different settings but exact benefit remains unclear [38, 39]. Current randomized trials are suggesting the role of combination chemotherapy in advanced and recurrent uterine leiomyosarcomas rather than with single-agent chemotherapy [40].

16.5.4 Surveillance

Due to its aggressive nature and high risk for recurrence, a surveillance consisting of detailed history, examination and imaging of chest, abdomen, and pelvis is recommended every 3 months for 2 years followed by every 6–12 months for the next 3 years as per the National Comprehensive Cancer Network guidelines [41].

16.6 Endometrial Stromal Tumors

Endometrial stromal tumors are less common uterine sarcomas with cytological and architectural features reminiscent of endometrial stromal cells [42].

According to 2014 WHO classification system, endometrial stromal tumors are classified as follows [43]:

- Endometrial stromal nodule (ESN)
- Low-grade endometrial stromal sarcoma (LG-ESS)
- High-grade endometrial stromal sarcoma (HG-ESS)
- Undifferentiated uterine sarcoma (UUS)

Histologically, endometrial stromal sarcomas are classified by their invasion into the myometrium and the degree of differentiation, immunostaining, and genetic profiling have a distinguishing role in diagnosis.

16.6.1 Endometrial Stromal Nodule

They are the least common type of ESS [44] and can be grossly confused with a leiomyoma [45]. ESN typically are well-circumscribed, however, focal projections up to 2–3 mm into the myometrium can be seen [46].

16.6.2 Low Grade-ESS

They are low-grade sarcomas and are typically composed of uniform cells like endometrial stroma and have myometrial or vascular invasion. ESSs can have some features of myxoid changes, fibroblastic and/or smooth muscle differentiation, epithelioid changes, and extensive endometrioid glandular differentiation, which can create confusion in the diagnosis [47, 48]. In tumors with focal smooth muscle differentiation, if the component of smooth muscle is less than 30% it is classified as LG-ESS, but in tumors with a larger percentage, it is classified as mixed endometrial stromal and smooth-muscle neoplasm [45].

16.6.3 High Grade-ESS

High grade-ESS confers a subgroup of malignant ESS which have high-grade nuclear atypia with typically more destructive growth pattern with extensive myometrial invasion, necrosis, lymphovascular invasion, and mitotic activity >10 per 10 high-power fields [45]. These tumors display either:

1. A combination of low-grade and undifferentiated areas.
2. Cytologic and immunohistochemical features that are intermediate between classic low-grade ESS and undifferentiated endometrial stroma (UES).
3. Cytologic features of UES but with the presence of finger-like infiltrative pattern of the surrounding myometrium or extension into lymphovascular spaces.

The prognosis with HG-ESS is worse than with LG-ESS but better than undifferentiated uterine sarcoma [49].

16.6.4 Undifferentiated Uterine Sarcoma

UUS is typically differentiated by marked cytologic atypia, nuclear pleomorphism, high mitotic activity, and extensive invasion. They are typically seen in women over 50 years of age and have a very high recurrence rate and are almost always fatal [50].

16.6.5 Diagnosis

Diagnosis is made on clinical suspicion as described above. On imaging, a characteristic pattern of low-grade endometrial stromal sarcoma (LG-ESS) consists of worm-like projections in the vessels or along ligaments seen on MRI with diffusion weighted imaging [51].

16.6.6 Molecular Pathology

ESN and LG-ESS are mostly immune-reactive for ER and PR receptors, positive for CD10, smooth muscle actin and are negative for h-caldesmon and histone deacetylase 8 such as the t (7;17) translocation, resulting in the expression of a fusion protein composed of two zinc finger genes (JAZF1 and JJAZ1) [52, 53]. These characteristics help in differentiation LG-ESS from other uterine sarcomas.

HG-ESS shows a strong diffuse cyclin D1 positivity [45] and expression of BCOR (BCL6 corepressor) [54] but can be negative for CD10, ER and PR. Those ones that exhibit c-kit, are associated with a poorer prognosis [55]. Rearrangements involving t(10;17) are frequently identified in these tumors and result in a 14-3-3 fusion to FAM22 [56].

UUS can have variable staining with ER, PR, and CD10 [45]. In those cases with cyclin D1 positivity, CD 10 is typically positive, which can help differentiate from HG-ESS, which are cyclin D1 positive but CD10 negative.

16.6.7 Treatment

16.6.7.1 Low-grade ESS

Surgery

Uterine-confined disease is best managed by staging surgery including a total hysterectomy with bilateral salpingo-oophorectomy. Bilateral oophorectomy is indicated as it is a hormone-sensitive tumor.

Lymph nodal metastasis is uncommon in low-grade sarcomas around 7–9%, hence the role of lymphadenectomy is not very well defined [57]. Studies have not shown a survival benefit with lymphadenectomy with LG-ESS [57, 58]. Another study found that there were no statistically significant differences in the 5-year survival rate between node-positive LG-ESS and node-negative LG-ESS (86% vs. 95%) [59].

In women who desire to preserve their fertility, conservative surgery in form of hysteroscopic resection or myomectomy is an option followed by high-dose progestogen therapy for 6 months. Two small series of 5 and 19 cases showed that three uterine reconstruction patients and five myomectomy patients finally had a successful birth and concluded that fertility-sparing treatment might be suitable in highly selected younger women with LG-ESS, who show a clear border and could be removed by complete en bloc resection [60, 61]. However, once family is completed hysterectomy with BSO is recommended as low-grade ESS has late recurrences [61].

Cases in which extrauterine disease is present, the role of surgery is questionable, especially, in cases where residual tumor is left after surgery [62]. Surgical staging and cytoreduction are to be done in cases of extrauterine disease only when the disease is completely resectable.

Adjuvant Therapy

For endometrial stromal nodule, hysterectomy alone is sufficient. In cases of LG-ESS, for stage I disease, surveillance alone is sufficient. For stages II to IV, given the high rates of expression of Estrogen Receptor (ER) and Progesterone Receptor (PR), endocrine therapy in the form of megestrol acetate (160 mg daily) [63] and medroxyprogesterone (250 mg daily) [64] has been recommended. A Phase II study showed that single-agent mifepristone in the management of LG-ESS could result in a stable disease rate of 50% [65]. Aromatase inhibitors (AI); Exemestane Type I AI or letrozole and anastrozole Type II AIs, play an important therapeutic role in adjuvant treatment. One retrospective study evaluated the effect of AIs in the management of 16 ESS patients, and found an overall response rate of 67% (60% partial response rate, 7% complete response rate) and a 20% stable disease rate in these patients [66].

Given the indolent nature of LG-ESS, the propensity for long-term survival (without adjuvant treatment), and the potential complications of radiotherapy (RT) including fibrosis, stricture, fistula, and second malignancies, the role of RT should be individualized, taking into account the risks and benefits of treatment.

Long-term follow-up is recommended in low-grade ESS even in Stage 1 disease as recurrences can occur after 10–20 years after the initial diagnosis. Stage is the most significant prognostic factor, and 5-year overall survival (OS) rate for Stage I patients is more than 90%, but decreased to 50% for Stage III and IV [67]. The most common sites for recurrence are pelvis and abdomen. Due to localized nature of recurrences, surgical resection followed by adjuvant treatment can be considered, however, there is a lack of evidence to support it.

16.6.7.2 High-grade ESS and Undifferentiated Sarcoma

The treatment of choice is hysterectomy and BSO. Role of lymphadenectomy is not certain as majority of recurrences are in visceral sites, however, in the case of extensive disease lymphadenectomy is recommended if feasible and may have a survival advantage [68]. In case of recurrences, metastasectomy should be considered as for other sarcomas.

For patients with HG-ESS and UUS, systemic therapy should be considered for patients with stage II and above.

For stage I disease, the benefit of addition of chemotherapy in the form of doxorubicin and ifosfamide or gemcitabine plus docetaxel and doxorubicin is designated as category 2B [69].

Radiation therapy can be considered for those in stage II onward along with chemotherapy as it has shown to reduce locoregional recurrence although has not shown to have a survival advantage [69, 70]. Addition of chemotherapy in the SARCGYN study has shown an increased 3-year disease-free survival rate (55% vs. 41%, $p = 0.048$) with a nonstatistical improvement in 3-year OS (81% vs. 69%) [71].

High-grade ESS has a poorer prognosis with a median progression-free survival (PFS) and OS ranging from 7 to 11 months and 11 to 23 months, respectively [72].

16.6.7.3 Adenosarcoma

Adenosarcoma is a low-grade, rare neoplasm in which there are a benign epithelial process and a malignant stromal element. Most of these tumors arise from the endometrium, but they have also been seen arising from the lower uterine segment, myometrium, and endocervix or extrauterine Mullerian tissues [73]. Adenosarcomas typically express positivity for CD10 and Wilms' tumor (WT-1), ER, PR, androgen receptor (AR), smooth muscle actin (SMA), cytokeratin, and desmin and alterations in PIK3CA/AKT/PTEN pathway are seen in 72%. Although, those cases in which there is stromal overgrowth, hormonal receptors are negative [74].

They are managed as per the lines of LG-ESS and role of adjuvant radiation, chemotherapy, or hormone therapy is not well established [75].

16.7 Targeted Therapy in Uterine Sarcoma

Currently, evidence from tumor biology has found that these tumors showed alternation and/or mutation of genomes and the intracellular signal pathway. Many Phase III studies with pazopanib, regorafenib, muramyl tripeptide, and ridaforolimus are still ongoing [76]. Other promising agents that are still in earlier stages of development such as CDK4 and MDM2 inhibitors, cediranib, eribulin, and crizotinib, are also being tested [77].

16.8 Conclusion

To conclude, it is difficult to establish a preoperative diagnosis of sarcoma and the diagnosis is made postoperatively on histopathology after surgery for uterine fibroids. Hysterectomy with bilateral salpingo-oophorectomy is the mainstay of treatment for sarcomas and the role of lymphadenectomy is not much proven as majority of metastasis are visceral due to hematogenous spread of the tumor. Only bulky lymph nodes should be removed. Radiation therapy and chemotherapy can be used in advanced stages and targeted therapy holds much promise in the treatment of sarcomas.

Key Points

- The presenting symptoms of uterine sarcomas are abnormal vaginal bleeding and less commonly an abdominopelvic mass. A rapidly enlarging pelvic mass, especially in a postmenopausal female should be evaluated for malignancy.
- Preoperative endometrial assessment (pipelle or dilation and curettage) is limited in the diagnosis of uterine sarcomas. Studies have reported high accuracy rates in predicting uterine leiomyosarcomas using serum LDH levels and diffusion weighted MRI.
- Surgery including total hysterectomy and bilateral salpingo-ophorectomy is the cornerstone of management of uterine sarcomas. Ovarian conservation may be considered in young premenopausal women without compromising overall survival. Routine regional lymphadenectomy is not recommended for uterine sarcomas, but bulky nodes should be resected.
- Surgical cytoreduction is recommended in advanced cases of uterine sarcomas – including uLMS and ESS, since they do not respond well to chemotherapy or radiotherapy and may be considered in recurrent cases. Routine adjuvant radiotherapy is not recommended for early stage uLMS. For advanced stages, radiotherapy needs to be individualized depending on the pathological findings.
- Because of the increased risk of relapse, NCCN recommends adjuvant chemotherapy with or without radiotherapy in completely resected Stage II and above uLMS and UUS. It is also recommended in incompletely resected or metastatic

disease. The most active drugs used in advanced or recurrent uLMS are Gemcitabine/Docetaxel and Doxorubicin.

- There is no data to support adjuvant chemotherapy in women with uterus-confined low grade ESS after complete resection. These patients are managed by observation and close surveillance. Post-operative hormonal therapy is advocated in stages II-IV low grade ESS (Category 2A recommendation). Hormonal therapy is also used for recurrent or metastatic low grade ESS lesions.

References

1. Shah SH, Jagannathan JP, Krajewski K, O'Regan KN, George S, Ramaiya NH. Uterine sarcomas: then and now. AJR Am J Roentgenol. 2012;199:213–23.
2. Tumors of the uterine corpus. In: Tavassoli FA, Devilee P, eds. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of the Breast and Female Genital Organs. Lyons: IARC Press; 2003:217–258.
3. McCluggage WG. Uterine carcinosarcomas (malignant mixed Mullerian tumors) are metaplastic carcinomas. Int J Gynecol Cancer. 2002;12:764–7.
4. Mutter GL, Prat J, editors. Pathology of the female reproductive tract. 3th ed. London: Churchill Livingstone Elsevier; 2014.
5. Wen KC, Horng HC, Wang PH, Chen YJ, Yen MS, Ng HT. Taiwan Association of Gynecology Systematic Review Group. Uterine sarcoma Part I-Uterine leiomyosarcoma: The Topic Advisory Group systematic review. Taiwan J Obstet Gynecol. 2016;55(4):463–71.
6. Hosh M, Antar S, Nazzal A, Warda M, Gibreel A, Refky B. Uterine sarcoma: analysis of 13,089 cases based on surveillance, epidemiology, and end results database. Int J Gynecol Cancer. 2016;26(6):1098–104.
7. Giuntoli 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;89:460–9.
8. Lavie O, Barnett-Griness O, Narod SA, et al. The risk of developing uterine sarcoma after tamoxifen use. Int J Gynecol Cancer. 2008;18:352–6.
9. Jaakkola S, Lyytinen HK, Pukkala E, et al. Use of estradiol-progestin therapy associates with increased risk for uterine sarcomas. Gynecol Oncol. 2011;122:260–3.
10. Schwartz SM, Thomas DB. A case-control study of risk factors for sarcomas of the uterus. The world health organization collaborative study of neoplasia and steroid contraceptives. Cancer. 1989;64(12):2487–92.
11. Nilbert M, Therkildsen C, Nissen A, Akerman M, Bernstein I, et al. Sarcomas associated with hereditary nonpolyposis colorectal cancer: broad anatomical and morphological spectrum. Familial Cancer. 2009;8:209–13.
12. Francis JH, Kleinerman RA, Seddon J, et al. Increased risk of secondary uterine leiomyosarcoma in hereditary retinoblastoma. Gynecol Oncol. 2012;124:254–9.
13. D'Angelo E, Prat J. Uterine sarcomas: a review. Gynecol Oncol. 2010;116:131–13.
14. Leung F, Terzibachian JJ. The impact of tumor morcellation during surgery on the prognosis of patients with apparently early uterine leiomyosarcoma. Gynecol Oncol. 2012;124:172.
15. Jones MW, Norris HJ. Clinicopathologic study of 28 uterine leiomyosarcomas with metastases. Int J Gynecol Pathol. 1995;14:243–9.
16. Karpathiou G, Sivridis E, Giatromanolaki A. Myxoid leiomyosarcoma of the uterus: a diagnostic challenge. Eur J Gynaecol Oncol. 2010;31:446.
17. Leitao MM Jr, Hensley M, Barakat RR, et al. Immunohistochemical expression of estrogen and progesterone receptors and outcomes in patients with newly diagnosed uterine leiomyosarcoma. Gynecol Oncol. 2012;124:558–62.

18. Ioffe YJ, Li AJ, Walsh CS, et al. Hormone receptor expression in uterine sarcomas: prognostic and therapeutic roles. Gynecol Oncol. 2009;115:466–71.
19. Rodriguez Y, Baez D, de Oca FM, et al. Comparative analysis of the ERa/ERb ratio and neurotensin and its high-affinity receptor in the myometrium, uterine leiomyoma, atypical leiomyoma, and leiomyosarcoma. Int J Gynecol Pathol. 2011;30:354–63.
20. Lee CH, Roh J, Choi J, et al. Cyclooxygenase-2 is an independent predictor of poor prognosis in uterine leiomyosarcomas. Int J Gynecol Cancer. 2011;21:668–72.
21. Van den Bosch T, Dueholm M, Leone FP, Valentin L, Rasmussen CK, Votino A, et al. Terms, definitions and measurements to describe sonographic features of myometrium and uterine masses: a consensus opinion from the Morphological Uterus Sonographic Assessment (MUSA) group. Ultrasound Obstet Gynecol. 2015;46(3):284–98.
22. Rha SE, Byun JY, Jung SE, et al. CT and MRI of uterine sarcomas and their mimickers. AJR Am J Roentgenol. 2003;181:1369.
23. Lin G, Yang LY, Huang YT, Ng KK, Ng SH, Ueng SH, et al. Comparison of the diagnostic accuracy of contrast-enhanced MRI and diffusion-weighted MRI in the differentiation between uterine leiomyosarcoma/smooth muscle tumor with uncertain malignant potential and benign leiomyoma. J Magn Reson Imaging. 2016;43(2):333–42.
24. Lee WL, Yuan CC, Wang PH. Positron emission tomography and uterine leiomyomas. Gynecol Oncol. 2007;107(3):593–4.
25. Bansal N, Herzog TJ, Burke W, et al. The utility of preoperative endometrial sampling for the detection of uterine sarcomas. Gynecol Oncol. 2008;110:43.
26. Nagai T, Takai Y, Akahori T, et al. Novel uterine sarcoma preoperative diagnosis score predicts the need for surgery in patients presenting with a uterine mass. Springer Plus. 2014;3:678.
27. Ducie JA, Leitao MM Jr. The role of adjuvant therapy in uterine leiomyosarcoma. Expert Rev Anticancer Ther. 2016;16(1):45–55.
28. Nasioudis D, Chapman-Davis E, Frey M. Safety of ovarian preservation in premenopausal women with stage I uterine sarcoma. J Gynecol Oncol. 2017;28:e46.
29. Takamizawa S, Minakami H, Usui R, et al. Risk of complications and uterine malignancies in women undergoing hysterectomy for presumed benign leiomyomas. Gynecol Obstet Investig. 1999;48:193.
30. Parker WH, Fu YS, Berek JS. Uterine sarcoma in patients operated on for presumed leiomyoma and rapidly growing leiomyoma. Obstet Gynecol. 1994;83:414.
31. Denschlag D, Ackermann S, Battista MJ, Cremer W, Egerer G, Follmann M, et al. Sarcoma of the Uterus. Guideline of the DGGG and OEGGG (S2k Level, AWMF Register Number 015/074, February 2019). Geburtshilfe Frauenheilkd. 2019;79(10):1043–60.
32. Sagae S, Yamashita K, Ishioka S, et al. Preoperative diagnosis and treatment results in 106 patients with uterine sarcoma in Hokkaido, Japan. Oncology. 2004;67:33.
33. Dinh TA, Oliva EA, Fuller AF Jr, et al. The treatment of uterine leiomyosarcoma. Results from a 10-year experience (1990–1999) at the Massachusetts General Hospital. Gynecol Oncol. 2004;92:648.
34. Park JY, Kim DY, Suh DS, et al. Prognostic factors and treatment outcomes of patients with uterine sarcoma: analysis of 127 patients at a single institution, 1989–2007. J Cancer Res Clin Oncol. 2008;134:1277.
35. Duffaud F, Ray-Coquard I, Salas S, Pautier P. Recent advances in understanding and managing leiomyosarcomas. F1000Prime Rep. 2015 May 12;7:55.
36. Hensley ML, Enserro D, Hatcher H, et al. Adjuvant gemcitabine plus docetaxel followed by doxorubicin versus observation for high-grade uterine leiomyosarcoma: a phase III NRG oncology/gynecologic oncology group study. J Clin Oncol. 2018:JCO1800454.
37. Reed NS, Mangioni C, Malmström H, 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;44:808.
38. 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.

39. Hensley ML, Ishill N, Soslow R, et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: results of a prospective study. Gynecol Oncol. 2009;112:563.
40. Kanjeekal S, Chambers A, Fung MF, et al. Systemic therapy for advanced uterine sarcoma: a systemic review of the literature. Gynecol Oncol. 2005;97:624–37.
41. National Comprehensive Cancer Network (NCCN). NCCN Clinical practice guidelines in oncology. Available from https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Accessed on July 22, 2019.
42. Chan JK, Kawar NM, Shin JY, et al. Endometrial stromal sarcoma: a population-based analysis. Br J Cancer. 2008;99:1210.
43. Conklin CM, Longacre TA. Endometrial stromal tumors: the new WHO classification. Adv Anat Pathol. 2014;21:383.
44. Fdili Alaoui FZ, Chaara H, Bouguern H, et al. Endometrial stromal nodule: report of a case. Case Rep Med. 2011;2011:260647.
45. Oliva E, Carcangiu ML, Carinelli SG, et al. Chapter 5: Tumours of the uterine corpus: mesenchymal tumors. In: Kurman RJ, Carcangiu ML, Herrington CS, Young RH, editors. WHO classification of tumours of female reproductive organs. 4th ed. Lyon: International Agency for Research on Cancer; 2014. p. 136.
46. Ryuko K, Takahashi K, Miyazaki K. A case of endometrial stromal nodule. Shimane J Med Sci. 1996;14:27–8.
47. Oliva E, Young RH, Clement PB. Myxoid and fibrous endometrial stromal tumors of the uterus: a report of 10 cases. Int J Gynecol Pathol. 1999;18:310–9.
48. 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;26:1142–50.
49. Lee CH, 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.
50. Evans HL. Endometrial stromal sarcoma and poorly differentiated endometrial sarcoma. Cancer. 1982;50:2170–82.
51. Tamai K, Koyama T, Saga T, et al. The utility of diffusion-weighted MR imaging for differentiating uterine sarcomas from benign leiomyomas. Eur Radiol. 2008;18:723.
52. Chiang S, Ali R, Melnyk N, et al. Frequency of known gene rearrangements in endometrial stromal tumors. Am J Surg Pathol. 2011;35:1364.
53. Koontz JI, Soreng AL, Nucci M, et al. Frequent fusion of the JAZF1 and JJAZ1 genes in endometrial stromal tumors. Proc Natl Acad Sci USA. 2001;98:6348.
54. Chiang S, Lee CH, Stewart CJR, et al. BCOR is a robust diagnostic immunohistochemical marker of genetically diverse high-grade endometrial stromal sarcoma, including tumors exhibiting variant morphology. Mod Pathol. 2017;30:1251.
55. 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;95:632.
56. Kruse AJ, Croce S, Kruitwagen RF, et al. Aggressive behavior and poor prognosis of endometrial stromal sarcomas with YWHAE-FAM22 rearrangement indicate the clinical importance to recognize this subset. Int J Gynecol Cancer. 2014;24:1616.
57. Chan JK, Kawar NM, Shin JY, Osann K, Chen LM, Powell CB, et al. Endometrial stromal sarcoma: a population-based analysis. Br J Cancer. 2008;99:1210–5.
58. Lange SS, Novetsky AP, Powell MA. Recent advances in the treatment of sarcomas in gynecology. Discov Med. 2014;18:133–40.
59. Shah JP, Bryant CS, Kumar S, Ali-Fehmi R, Malone JM Jr, Morris RT. Lymphadenectomy and ovarian preservation in low-grade endometrial stromal sarcoma. Obstet Gynecol. 2008;112:1102–8.

60. Jin Y, Li Y, Deng CY, Tian QJ, Chen H, Pan LY. Fertility-sparing treatment of low-grade endometrial stromal sarcoma. Int J Clin Exp Med. 2015;8:5818–21.
61. Bai H, Yang J, Cao D, Huang H, Xian Y, Wu M, et al. Ovary and uterus-sparing procedures for low-grade endometrial stromal sarcoma: a retrospective study of 153 cases. Gynecol Oncol. 2014;132:654–60.
62. Leath CA 3rd, Huh WK, Hyde J Jr, et al. A multi-institutional review of outcomes of endometrial stromal sarcoma. Gynecol Oncol. 2007;105:630.
63. Chu MC, Mor G, Lim C, et al. Low-grade endometrial stromal sarcoma: hormonal aspects. Gynecol Oncol. 2003;90:170.
64. Amant F, De Knijf A, Van Calster B, et al. Clinical study investigating the role of lymphadenectomy, surgical castration and adjuvant hormonal treatment in endometrial stromal sarcoma. Br J Cancer. 2007;97:1194.
65. Ramondetta LM, Johnson AJ, Sun CC, Atkinson N, Smith JA, Jung MS, et al. Phase 2 trial of mifepristone (RU-486) in advanced or recurrent endometrioid adenocarcinoma or low-grade endometrial stromal sarcoma. Cancer. 2009;115:1867–74.
66. Altman AD, Nelson GS, Chu P, Nation J, Ghatage P. Uterine sarcoma and aromatase inhibitors: Tom Baker Centre experience and review of the literature. Int J Gynecol Cancer. 2012;22:1006–12.
67. Prat J, Mbatani N. Uterine sarcomas. Int J Gynecol Obstet. 2015;131:S105–S10.
68. Horng HC, Wen KC, Wang PH, Chen YJ, Yen MS, Ng HT. Taiwan Association of Gynecology Systematic Review Group. Uterine sarcoma Part II-Uterine endometrial stromal sarcoma: The TAG systematic review. Taiwan J Obstet Gynecol. 2016 Aug;55(4):472–9.
69. Rizzo A, Pantaleo MA, Saponara M, Nannini M. Current status of the adjuvant therapy in uterine sarcoma: a literature review. World J Clin Cases. 2019;7(14):1753–63.
70. Reed NS, Mangioni C, Malmström H, Scarfone G, Poveda A, Pecorelli S, et al. Phase III randomized study to evaluate the role of adjuvant pelvic radiotherapy in the treatment of uterine sarcomas Stages I and II: A European Organization for Research and Treatment of Cancer Gynecological Cancer Group study (protocol 55874). Eur J Cancer. 2008;44:808–18.
71. Pautier P, Floquet A, Gladieff L, Bompas E, Ray-Coquard I, Piperno-Neumann S, et al. A randomized clinical trial of adjuvant chemotherapy with doxorubicin, ifosfamide, and cisplatin followed by radiotherapy versus radiotherapy alone in patients with localized uterine sarcomas (SARCGYN study). A study of the French Sarcoma Group. Ann Oncol. 2013;24:1099–104.
72. Pautier P, Nam EJ, Provencher DM, Hamilton AL, Mangili G, Siddiqui NA, et al. Gynecologic Cancer Inter Group (GCIG) consensus review for high-grade undifferentiated sarcomas of the uterus. Int J Gynecol Cancer. 2014;24:S73–S7.
73. Clement PB, Scully RE. Mullerian adenosarcoma of the uterus: a clinicopathologic analysis of 100 cases with a review of the literature. Hum Pathol. 1990;21:363–81.
74. Gallardo A, Prat J. Mullerian adenosarcoma: a clinicopathologic and immunohistochemical study of 55 cases challenging the existence of adenofibroma. Am J Surg Pathol. 2009;33:278–88.
75. Kaku T, Silverberg SG, Major FJ, et al. Adenosarcoma of the uterus: a Gynecologic Oncology Group clinicopathologic study of 31 cases. Int J Gynecol Pathol. 1992;11:75.
76. Martin-Liberal J, Benson C, Judson I. New drugs in sarcomas. Expert Opin Pharmacother. 2014;15:221–9.
77. Yen MS, Chen JR, Wang PH, Wen KC, Chen YJ, Ng HT. Taiwan Association of Gynecology Systematic Review Group. Uterine sarcoma part III-Targeted therapy: The Taiwan Association of Gynecology (TAG) systematic review. Taiwan J Obstet Gynecol. 2016;55(5):625–34.

Uterine Smooth Muscle Tumors of Uncertain Malignant Potential (STUMP)

17

Sumita Mehta and Ankita Mann

17.1 Introduction

Smooth muscle tumors of the uterus are classified as leiomyoma or leiomyosarcoma based on their histological features including mitotic activity, cytological atypia, and coagulative tumor necrosis. According to Worldhealth Organization (WHO), STUMP is a heterogenous group of smooth muscle tumors, which cannot be clearly categorized as benign or malignant [1]. The term STUMP was first used by Kempson in 1973 to describe such tumors [2]. STUMP can recur or metastasize to distant sites and so they are described as tumors with low malignant potential. As STUMP is a rare tumor so its incidence is not well known but among women undergoing hysterectomy or myomectomy for a preoperative diagnosis of leiomyoma, STUMP is seen in 0.01% of histological specimens [3]. Due to limited data on its malignant potential, the management of STUMP is controversial.

17.2 Pathophysiology

Stem cells present in the normal myometrial tissue control its proliferation and self-renewal in a regulated manner. Cells undergo multiple cycles of growth and involution under the effect of ovarian hormones estrogen and progesterone [4, 5]. Indirect paracrine signals also control the myometrial cells and are responsible for proliferation of smooth muscle cells of uterus. Repeated hormonal and paracrine signals can then create genetic mutations and chromosomal rearrangements in myometrial stem cells, which lead to unregulated proliferation and growth [5]. Some of the mutations involve the mediator complex subunit12 (MED12), T-cell transcription factor (TGF), and transforming growth factor B3 (TGF B3) [6]. Deletions of 1p have been

S. Mehta (✉) · A. Mann
Department of Obstetrics & Gynecology, Babu Jagjivan Ram Memorial Hospital, New Delhi, India

S. Mehta, B. Gupta (eds.), *Recent Advances in Endometrial Cancer*,
https://doi.org/10.1007/978-981-15-5317-2_17

shown to be associated with possible malignant progression of leiomyomas [6, 7]. Leiomyomas with mutations of high mobility group AT-hook 2 (HMGA2) which promotes tumorigenesis through PLAG1 activation or ones with accumulation of fumarate also have a propensity to develop into STUMP or leiomyosarcomas [6]. More research is still needed to elicit the molecular changes that cause a leiomyoma to develop into STUMP.

17.3 Classification

The classification of smooth muscle cell malignancies of uterus remains controversial and it is challenging to differentiate STUMP from various variants of leiomyoma or leiomyosarcoma. They are generally differentiated on the basis of cytological atypia, mitotic rate, and presence or absence of tumor cell necrosis [8].

Kempson and Hendrickson originally gave diagnostic criteria for evaluation of smooth muscle tumors of the uterus as shown in Table 17.1 [2].

If tumor necrosis and moderate to severe atypia are present whatever be the mitotic index, tumor is leiomyosarcoma (LMS).

The histological classification was given by Bell et al. in 1994 and these criteria have been validated by WHO in 2003 [9]. The criteria include:

Nuclear atypia: Severity depends on the presence of nuclear pleomorphism, nuclear size, chromatin density, nuclear membrane irregularities, and prominence of nucleoli.

Mitotic index: It represents number of mitotic figures per 10 high power field (hpf). The following features should be looked for:

- Hairy extension of chromatin must be present.
- Nuclear membrane must be absent but cytoplasm can be distinguished.
- Presence of lymphocytes, mast cells, degenerated cells, and hematoxylin can be seen.

Presence or absence of coagulative tumor necrosis (CTCN): This is the most important feature in assessing STUMP tumors. In CTCN, there is an abrupt transition between normal and necrotic cells without any intervening zone of hyalinized or granulation tissue. Also, cell outlines and nuclei are preserved to the extent that hyperchromasia and pleomorphism can still be made out in the nuclei. Ghost outlines of the tumor cells can be seen in the necrotic areas. Hemorrhage is generally absent in the necrosis. The prognostic value of CTCN is very high and effort should

Table 17.1 Diagnostic criteria for classification of smooth muscle tumors of uterus [2]

	Mitotic index	Tumor necrosis	Cellular atypia
Leiomyoma	Absent	Absent	Absent or mild
Leiomyosarcoma	>10 mitotic/10 hpf	Absent	Moderate to severe
Atypical leiomyoma	< 10 mitotic/10 hpf	Absent	Moderate to severe

be made to differentiate it from other types of benign morphologic changes like hyalinizing necrosis and necrosis associated with hemorrhage and superficial ulceration. Another type of necrosis commonly seen in leiomyomas is infarct-type necrosis and this must be differentiated from CTCN. Infarct-type necrosis is usually associated with a zone of fibrous or granulation tissue between the viable and necrotic tissue, which is absent in CTCN.

The Stanford criteria for the histologic diagnosis of leiomyosarcoma includes at least two of the following criteria: diffuse moderate to severe atypia, a mitotic count of at least 10 mitotic figures and coagulative tumor cell necrosis; absence of necrosis and atypia and <4 mitosis indicate benign leiomyoma. WHO classifies that a uterine smooth muscle tumor that cannot be unequivocally categorized as benign or malignant should be defined as STUMP. Ip et al. in their study described 16 tumors in 11 hospitals between 1992 and 2002. They concluded that STUMP should be diagnosed when a tumor shows any unusual combination of the 3 above-mentioned features but does not satisfy the Stanford criteria for leiomyosarcoma [10].

Bell et al. subclassified STUMP under the following categories [8]:

- *Smooth muscle with low malignant potential*: Mitotic index <10 mitotic figures/10 hpf, coagulative necrosis is present and no atypia to mild atypia seen.
- *Atypical leiomyoma but limited experience:* Mitotic index <20 mitotic figures/10 hpf, coagulative necrosis is absent, severe atypia is seen.
- *Atypical leiomyoma with low risk of recurrence:* Mitotic index <10 mitotic figures/10 hpf, coagulative necrosis is absent, diffuse moderate to severe atypia is present.

Guntupalli et al. diagnosed STUMP when the tumor fitted into one of the following criteria:

- Tumor necrosis (+), no atypia, mitosis ≤10/10 HPF.
- Diffuse atypia (+), no tumor necrosis, mitosis ≤10/10 HPF.
- No tumor necrosis, no atypia, mitosis ≥20/10 HPF.
- Cellularity or hypercellularity with mitosis ≥4/10 HPF.
- Irregular margins or vascular invasion in peripheral side of tumor [11].

Deodhar et al. reviewed STUMP and atypical leiomyoma and concluded that CTCN is crucial to the diagnosis and a correlation with imaging is important, especially if necrosis is not seen on biopsy [12]. Xiropotamou ON et al. also found coagulative necrosis the most strongly associated factor with malignant behavior of STUMP [13].

17.4 Clinical Features

Women with STUMP tumors have symptoms similar to fibroids and the most common clinical features include abnormal vaginal bleeding, rapidly growing pelvic mass, pelvic pain, or symptoms secondary to compression and anemia [10].

As the condition is rare, so demographic data are limited but the age of onset of the disease is similar to leiomyoma or leiomyosarcoma and the mean age at presentation is 43 years [11].

Joseph et al. reviewed 18 cases of STUMP and found pelvic mass to be the most common presentation seen in 50% women and menorrhagia in 16.7% [14].

As the risk factors and biological events that lead to STUMP development are not well understood so the subsequent clinical behavior is also unpredictable [11].

17.5 Diagnosis

17.5.1 Imaging Techniques

Ultrasonography: Ultrasound imaging does not provide any specific diagnostic feature for differentiation of leiomyoma from its variants. However, the presence of vascularized mass with irregular outline or anechoic necrotic areas can point toward aggressive tumors like sarcoma.

Magnetic Resonance Imaging (MRI): MRI has been used to differentiate benign leiomyomas and LMS utilizing increased signal intensity, but evidence is still lacking to distinguish STUMP from leiomyoma. It is still the most sensitive imaging modality available to preoperatively diagnose LMS.

The MR characteristics of uterine leiomyomas are described as well-demarcated hypointense masses on T2 weighted images (T2WI). Mitotic figures and cytological atypia, which are features of STUMP cannot be demonstrated on MRI but high cellularity can be seen as hyperintense signal areas on T2WI [15]. Coagulative tumor necrosis which is commonly present in STUMP though cannot be directly appreciated on MRI but at times can be seen as intratumoral hemorrhage on MR appearing as hyperintense signal areas on T1W1 [16]. But if LMS or STUMP does not have any hemorrhage, then it is difficult to obtain a correct diagnosis.

Intensity signals on MRI diffusion-weighted imaging (DWI) and apparent diffusion coefficients (ADC) can differentiate leiomyoma from leiomyosarcoma. In a retrospective study by Sato et al. low-intensity lesions on (DWI) were leiomyoma whereas high and intermediate intensity signals were indicative of leiomyosarcoma [17].

Tanaka et al. in their study described MR findings in cases of LMS/STUMP. They concluded the MR findings in such cases as follows [16]:

- More than 50% of the lesion shows high signal T2WI.
- Any small area of high signal within tumor on T1WI.
- Presence of unenhanced pocket-like areas after contrast administration.

Bonneau et al. compared sonography and MR findings of leiomyoma and LMS/STUMP. They found the presence of single tumor, absence of acoustic shadowing, and presence of free fluid more commonly associated with LMS/STUMP [18].

Role of positron emission tomography (PET Scan) is limited as leiomyoma can take up FDG (fluorodeoxyglucose) on PET scan but differentiation between STUMP and sarcoma is still difficult.

17.5.2 Immunohistochemistry

There is no available data yet to formulate any recommendation regarding using immunohistochemistry for diagnosis of STUMP. The most commonly studied markers are p16, p21, p53, and Ki 67. Also, progesterone and estrogen receptors have recently been included in the armamentarium of diagnostic tests.

- p53: It is a suppressor gene found frequently in leiomyosarcomas. Increased frequency of p53 mutations in leiomyosarcoma was first reported by De Vos et al. [19]. Other authors found that though p53 expression was significantly high in leiomyosarcomas, the frequency of p53 positivity was not as high as expected. Also, the frequency of positive p53 has ranged from 13% to 56.5% in various studies [20, 21]. Nordal et al. did not find any association between p53 positivity and prognosis of the tumor [22]. According to Wang et al., p53 could be used as one of the criteria to distinguish malignant smooth muscle tumors of the uterus [23].
- p16: Overexpression of p16 is seen in leiomyosarcomas and found to be higher than leiomyomas. Chen et al. found strong and intermediate to diffuse staining pattern for p16 in all 100% cases of leiomyosarcoma and STUMP as opposed to only 14% of leiomyomas in their study; also the staining in leiomyomas was focal and weak [24].
- Atkins et al. in their study concluded that p16 is preferentially expressed by LMS and only rarely in leiomyoma and in the cases in which CTCN cannot be ascertained, addition of p16 can help to classify a subset of STUMP that should be classified as LMS [25]. In the study by Bodner-Adler et al., 57% of leiomyosarcomas expressed p16 compared to only 12% of leiomyomas. Also, 33% of STUMP expressed p16 but only focally [26].
- Ki-67: It is a nonhistone protein which is expressed in G1 phase of cell cycle and is an important proliferation marker. Overexpression of p53 and high Ki-67 labeling index are found in leiomyosarcoma and can be used to distinguish it from benign leiomyoma or STUMP [27]. Chen et al. in his study found that 83% of leiomyosarcomas had more than 10% of cells positive for Ki-67 as against none in leiomyomas, both the cases of STUMP in his study were positive for Ki-67 [24].
- Protein Bcl-2: This protein promotes cell replication and prevents apoptotic cell death. Additionally, bcl-2 also promotes cell replication by decreasing the requirement for growth factors and thus plays an important role in the growth of tumors. According to Bonder et al., Bcl-2 is expressed more frequently in leiomyomas than in LMS and STUMP. Also, tumors positive for Bcl-2 have a better prognosis with less vascular involvement and longer survival [26].

- Progesterone receptor (PR): Zhai et al. reported a strong positive staining for PR in all their cases of STUMP [28]. Various other authors have also found STUMP tumors to be positive for PR expression while detecting low immunostaining rates of PR in leiomyosarcomas [29, 30]. Gannon et al. and Atkins et al. compared the expression of progesterone (PR), p16, and p53 in leiomyoma, leiomyoma variants, and leiomyosarcoma [25, 31]. In their study, PR expression was seen in 82% to 100% leiomyoma, 75–90% leiomyoma variants, and <25% leiomyosarcoma indicating a significant difference in staining intensity while comparing STUMP with leiomyosarcoma.

The use of immunohistochemistry has a definite role in diagnosis and risk stratification of the tumors but its utility should be weighed against the cost of the tests.

17.6 Treatment

Since STUMP represents a rare group of neoplasms, consensus regarding their management and surveillance guidelines has not been reached yet.

Multidisciplinary team approach by gynecologist, pathologist, and oncologist is required for early detection of disease and to decide the treatment of choice and follow-up program.

Although STUMP are tumors with low malignant potential but their definitive diagnosis can be made by tissue sampling on hysteroscopy D&C or specimen after myomectomy or hysterectomy. Outcome is not affected by whether the initial surgery was myomectomy or hysterectomy. If a diagnosis of STUMP is made in a postoperative myomectomy surgical specimen, it does not warrant a reoperation and hysterectomy [32]. But such evidence must be interpreted with caution as only limited data is available regarding conservative treatment for STUMP. In his retrospective analysis of 41 women with STUMP, Guntupalli et al. did not find any differences in long-term outcome of patients who had undergone myomectomy or hysterectomy [11].

Once diagnosis of STUMP has been made patient should be counseled about nature of tumor, its recurrence either as STUMP or leiomyosarcoma, and fertility-preserving options. Hysterectomy must be performed unless fertility is desired. If uterus preservation is required for future fertility, then these subsets of women should be on strict follow-up protocol including 6 monthly evaluations in the first 5 years followed by annual surveillance for the next 5 years.

Although there are no National Comprehensive Cancer Network guidelines for STUMP but recommendations can be based on the guidelines for management of leiomyosarcoma. The recommendations include:

- If a patient has been diagnosed with STUMP after tissue sample from biopsy, hysterectomy is recommended. This is regardless of the route of hysterectomy which can be abdominal, vaginal, or laparoscopic.

- Patients with surgically removed STUMP lesions should have a baseline CT scan of the chest, abdomen, and pelvis. The patient needs to be followed up with routine physical examinations after surgery every 6 months for 5 years and then annually thereafter as recurrences often present as pelvic, abdominal, or pulmonary metastasis.
- If the patient had myomectomy for fertility preservation, then clinical examinations every 6 months after surgery with yearly MRI and chest X-ray should be done for the next 5 years. Once the woman completes her family, hysterectomy is recommended to prevent recurrences [33, 34].

17.7 Recurrence

Although STUMP is thought to be a tumor with low malignant potential but recurrences are known. The recurrence rates range from 8.7% to 11% according to the limited data which is available. It is plausible that some tumors thought to be STUMP might actually have been underdiagnosed leiomyosarcomas and conversely, some leiomyomas with unusual pathology may have been wrongly reported as STUMP [10]. It is important to correctly distinguish between leiomyosarcoma and STUMP as the former is a very aggressive tumor with early recurrences and metastasis while STUMP is associated with delayed recurrences. Zang et al. reviewed 127 patients with leiomyomas ranging from benign to malignant and found that 21% of STUMP had recurred on follow-up [35]. Ly et al. had similar results with 12% of atypical leiomyomas recurring on follow-up [36]. Guntupalli et al. had a recurrence rate of 7.3% among 41 patients during a mean follow-up of 45 months [11]. Deodhar et al. reviewed 21 patients with STUMP of which 1 patient had metastatic liver disease 3 years after the primary surgery [12]. Generally, STUMPs may recur as either STUMP or as LMS. The mainstay of treatment in case of recurrence is surgical excision. Role of adjuvant therapy in the form of pelvic irradiation, hormone treatment with progesterone, chemotherapy, or gonadotropin-releasing hormone analogue is not clear as the clinical course of the tumor was similar in absence of such treatment.

17.8 Metastasis

Metastasis of STUMP is rare but recently cases of distant metastasis have been reported and lungs are the most common metastatic site. Canciani et al. reported metastasis to the lungs 24 years after hysterectomy for STUMP [37]. A literature search by Miller et al. identified 57 cases of STUMP, which had metastasized to lungs [38]. Kostopoulos also reported a case of a woman who developed pulmonary metastasis 3 years after undergoing hysterectomy for menorrhagia with histopathological report of STUMP [39]. Various authors have also reported cases of STUMP tumor metastasizing to the humerus bone [40, 41].

Philip et al. in their review on uterine smooth muscle tumors opined that it would be clinically more useful to classify them as either tumors with or without recurrence and/or metastatic potential [42].

17.9 Role of Adjuvant Therapy

Surgery is the mainstay of treatment for STUMP. The role of adjuvant therapy is less researched and less clear. Due to low recurrence rates, there is generally no role of adjuvant hormonal treatment or chemotherapy [43–45]. Some authors have given hormonal suppression in premenopausal women to prevent disease progression if metastasis was found but as recurrences are usually amenable to surgical resection, so adjuvant therapies are not indicated [37]. There are also no follow-up protocols for women to be followed after treatment for STUMP. Ip et al. have suggested 6 monthly follow-ups for the initial five years followed by annual surveillance for the next five years [10]. According to Andrea et al., women who are hysterectomized are followed-up by clinical examination every 6 months followed by an annual total body CT scan whereas women who are treated by uterus sparing surgery undergo clinical and sonographic examination every six months and an annual pelvic MRI and chest X-ray [46].

17.10 Conclusion

STUMP is a rare tumor with a low malignant potential. Arriving at a diagnosis of STUMP is crucial and challenging and should be done after a thorough histopathological examination. Coagulative tumor cell necrosis is the critical component in diagnosis and clinical as well as imaging correlation is required before the final diagnosis of STUMP is made. The biological behavior and prognosis are difficult to predict in such cases and recurrences/metastasis have been reported. The future research on molecular genetics, immunohistochemistry, and biomarkers will be helpful in guiding the management of such tumors.

Key Points

1. Uterine STUMP is a heterogeneous group of tumors that are clinically benign with a low malignant potential.
2. Coagulative tumor cell necrosis(CTCN) is crucial to the histopathological diagnosis of STUMP. It is characterized by an abrupt transition from viable cells to tumor cells and the intervening area of fibrosis or granulation tissue is lacking.
3. The clinical presentation of STUMPs is similar to that of uterine leiomyomas and typically includes abnormal vaginal bleeding, pelvic pain, and pressure symptoms.
4. Final diagnosis of STUMP is on histopathology.

5. A multidisciplinary management composed of gynecologist, pathologist, and oncologist is mandatory for early detection and to establish the treatment of choice in women with STUMP.
6. Surgery forms the mainstay of treatment. The route of hysterectomy does not affect the long-term prognosis of the disease.
7. The disease is known to recur/metastasize and patients with STUMP should receive a long-term surveillance through clinical examination and imaging techniques.

References

1. Tavassoli FA, Devilee P. World Health Organization classification of Tumors: tumors of the breast and female genital organs. Lyon: International Agency for Research on Cancer Press; 2003. p. 236–9.
2. Kempson RL. Sarcomas and related neoplasms. In: Noris HJ, Hertig AT, Abel MR, editors. The uterus. Baltimore: Williams and Wilkins; 1973.
3. Picerno TM, Wasson MN, Gonzalez Rios AR, et al. Morcellation and the incidence of occult uterine malignancy: a dual institution review. Int J Gynecol Cancer. 2016;26(1):149–55.
4. Bulun SE. Uterine fibroids. N Engl J Med. 2013;369:1344–55.
5. Zivanoic O, Jacks LM, Lasonos A, Leitao MM, et al. A nomogram to predict post-resection 5-year overall survival for patients with leiomyosarcoma. Cancer. 2012;118:660–9.
6. Mehine M, Kaasinen E, Heinonen HR, Makinen N, Kampjarvi K, et al. Characterization of uterine leiomyomas by whole genome sequencing. PANS. 2015;113:1315–20.
7. Hodge JC, Pearce KE, Clayton AC, Taran FA, Stewart EA. Uterine cellular leiomyomata with chromosome 1p deletions represent a distinct entity. Am J Obstet Gynecol. 2014;210:572.
8. Bell SW, Kempson RL, Hendrickson MR. Problematic uterine smooth muscle neoplasms. A clinicopathologic study of 213 cases. Am J Surg Pathol. 1994 Jun;18(6):535–58.
9. Tavassoli FA, Devilee P. World health Organization classification of tumors: tumors of the breast and female genital organs. Lyon: IARC Press.
10. Ip PP, Tse KY, Tam KF. Uterine smooth muscle tumors other than the ordinary leiomyomas and leiomyosarcomas: a review of selected variants with emphasis on recent advances and unusual morphology that may cause concern for malignancy. Adv Anat Pathol. 2010 Mar;17(2):91–112.
11. Guntupalli SR, Ramirez PT, Anderson ML, Milam MR, Bodurka DC, Malpica A. Uterine smooth muscle tumor of uncertain malignant potential: a retrospective analysis. Gynecol Oncol. 2009;113(3):324–6.
12. Deodhar KK, Goyal P, Rekhi B, et al. Uterine smooth muscle tumor of uncertain malignant potential and atypical leiomyoma: a morphological study of these grey zones with clinical correlation. Indian J Pathol Microbiol. 2011;54:706–11.
13. Xiropotamou On, Tsili AC, Vrekousis TH et al. Uterine smooth muscle tumor of uncertain malignant potential: an entity difficult to diagnose. https://www.eurorad.org/case/12733.
14. Ng JSY, Han A, Chew SH, Low J. A clinicopathologic study of uterine smooth muscle tumor of uncertain malignant potential. Ann Acad Med Singap. 2010;39:625–8.
15. Yamashita Y, Torashima M, Takahashi M, et al. Hyperintense uterine leiomyoma at T2 weighted MR imaging: differentiation with dynamic enhanced MR imaging and clinical implications. Radiology. 1993;189:721–5.
16. Tanaka YO, Nishida M, Tsunoda H, Okamoto Y, Yoshikawa H. Smooth muscle tumors of uncertain malignant potential and leiomyosarcomas of the uterus: MR findings. J Magn Reson Imaging. 2004;20(6):998–1007.

17. Sato K, Yuasa N, Fujita M, Fukishima Y. Clinical application of diffusion weighted imaging for preoperative differentiation between uterine leiomyoma and leiomyosarcoma. Am J Obstet Gynecol. 2014;210:358.
18. Bonneau C, Thomasin-Naggaua I, Dechow S, Cortez A, et al. value of ultrasonography and MRI imaging for the characterization of uterine mesenchymal tumors. Acta Oster Gynecol Scand. 2014;93(3):261–5.
19. de Vos S, Wilczynski SP, Fleischhacker M. Koeffler. p53 alterations in uterine leiomyosarcomas versus leiomyomas. Gynecol Oncol. 1994 Aug;54(2):205–8.
20. Hong T, Shimada Y, Uchida S, Itami A, Li Z, Ding Y, Kaganoi J, Komoto I, Sakurai T, Imamura M. Expression of angiogenic factors and apoptotic factors in leiomyosarcoma and leiomyoma. Int J Mol Med. 2001 Aug;8(2):141–8.
21. Jeffers MD, Farquharson MA, Richmond JA, McNicol AM. p53 immunoreactivity and mutation of the p53 gene in smooth muscle tumors of the uterine corpus. J Pathol. 1995 Sep;177(1):65–70.
22. Nordal RR, Kristensen GB, Stenwig AE, Trope CG, Nesland JM. Immunohistochemical analysis of p53 protein in uterine sarcomas. Gynecol Oncol. 1998;70:45–8.
23. Wang M, Xu Y, Zhang T. Smooth muscle neoplasms of the uterus – a 51 cases study. Zhonghua Bing Li Xue Za Zhi. 1996;25:263–5.
24. Chen L, Yang B. Immunohistochemical analysis of p16, p53 and ki67 expression in uterine smooth muscle tumors. Int J Gynecol Pathol. 2008;27:326–32.
25. Atkins KA, Arronte N, DArus CJ, Rice LW. The use of p16 in enhancing the histologic classification of uterine smooth muscle tumors. Am J Surg Pathol. 2008;32:98–102.
26. Bodner K, Bodner-Adler B, Kimberger O, Czerwenka K, Mayerhofer K. Bcl-2 receptor expression in patients with uterine smooth muscle tumors: an immune-histochemical analysis comparing leiomyoma, uterine smooth muscle tumor of uncertain malignant potential, and leiomyosarcoma. J Soc Gynecol Investig. 2001;11:187–91.
27. Won HS, Chun HG, Lee K. Retroperitoneal smooth muscle tumor of uncertain malignant potential after hysterectomy: a case report. J Med Case Rep. 2011;5:214.
28. Zhai YL, Kobayashi Y, Mori A, Orii A, Nikaido T, Konishi I, et al. Expression of steroid receptors, Ki-67, and p53 in uterine leiomyosarcomas. Int J Gynecol Pathol. 1999;18:20–8.
29. Mittal K, Demopoulos RI. MIB-1 (Ki-67), p53, estrogen receptor, and progesterone receptor expression in uterine smooth muscle tumors. Hum Pathol. 2001;32:984–7.
30. Bodner K, Bodner-Adler B, Kimberger O, Czerwenka K, Mayerhofer K. Estrogen and progesterone receptor expression in patients with uterine smooth muscle tumors. Fertil Steril. 2004;81:1062–6.
31. Gannon BR, Manduch M, Childs TJ. Differential immunoreactivity of p16in leimyosarcomas and leiomyoma variants. Int J Gynecol Pathol. 2008;27:68–73.
32. Odunsi K, Pejovic T. Gynecological cancers multidisciplinary approach to diagnosis and treatment of uterine sarcoma. New York: Demos Publishing Company; 2013. p. 83–93.
33. Ayaz D, Diniz G, Kahraman DS, Sayhan S, Uncel M, et al. The evaluation of the caveolin-1 and At-rich interactive domain 1 alpha expressions in uterine smooth muscle tumors. Indian J Pathol Microbiol. 2016;59:301–4.
34. Vahedpoor Z, Khamechian T, Zandi N. STUMP mistaken with ovarian tumor mistaken with ovarian tumor in a female with polio. J Obstet Gynecol Cancer Res. 2017;2:e9425.
35. Zhang Q, Ubago J, Li L. Molecular analysis of 6 different types of uterine smooth muscle tumors: emphasis in atypical leiomyoma. Cancer. 2014;120:3165–77.
36. Ly A, Mills AM, McKenny JK. Atypical leiomyoma of the uterus: a clinicopathological study of 51 cases. Am J Surg Pathol. 2013;37:643–9.
37. Canciani GN, Burbos N, Duncan TJ, Lonsdale R, Nieto JJ. Late presentation of metastatic smooth muscle neoplasm of the uterus with low malignant potential. J Gynecol Oncol. 2012;23:69–71.
38. Miller J, Shoni M, Siegert C. Benign metastasizing leiomyomas to the lungs: an institutional case series and a review of the recent literature. Ann Thorac Surg. 2016;101:253–8.

39. Kotsupoulos IC, Barbetakis N, Asteriou C, et al. Uterine smooth muscle tumor of uncertain malignant potential: a rare cause of multiple pulmonary nodules. Indian J Med Paediat Oncol. 2012;33(3):176–8.
40. Kropp L, Siegal GP, Frampton GM, Rodriguez MG, McKee S, et al. Primary intraosseous smooth muscle tumor of uncertain malignant potential: original report and molecular characterization. Rare Tumors. 2016;4:2016–3613.
41. Shapiro A, Ferenczy A, Turcotte R, Bruchim I, Gotlieb WH. Uterine smooth muscle tumor of uncertain malignant potential metastasizing to the humerus as a high grade leiomyosarcoma. Gynecol Oncol. 2004;94:818–20.
42. Philip PC, Tse KY, Tam KF. Uterine smooth muscle tumors other than the ordinary leiomyomas and leiomyosarcomas: a review of selected variants with emphasis on recent advances and unusual morphology that may cause concern malignancy. Adv Anat Pathol. 2010;17(2):91–111.
43. Kalogiannidis I, Stavrakis T, Dagklis T, Petousis S, et al. A clinicopathological study of atypical leiomyomas: Benign variant leiomyoma or smooth muscle tumor of uncertain malignant potential. Oncol Lett. 2016;11:1425–8.
44. Peeters N, Hulbosch S, Ballaux F, Baekelandt J. STUMP: analysis of diagnoses and therapies illustrated by two case reports. Eur J Gynecol Oncol. 2016;37:367–73.
45. Rommel B, Holzmann C, Bullerdiek J. Malignant mesenchymal tumors of the uterus-time to advocate a genetic classification. Expert Rev Anticancer Ther. 2016;111:1155–66.
46. Andrea DA, Gizzo S, Musaro A, Quaranta M, Noventa M, et al. Uterine smooth muscle tumors of uncertain malignant potential (STUMP): pathology, follow-up and recurrence. Int J Clin Exp Pathol. 2014;7(11):8136–42.