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Overview of Endometrial Cancer, Risk Factors, Diagnosis, and Treatment Options

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Abstract: **Endometrial cancer, is tumor coming from the endometrium, is the most common gynecological tumor in industrialized nations, and its prevalence is increasing. The aim of this review paper was to focus on discussing and overview the most important aspects of Endometrial cancer which is the most common gynecological cancer, and to specifically discuss the risk factors associated with this type of cancer, diagnostic procedures, and finally treatments approaches. We conducted a comprehensive search for articles published in English up to 2016. Search was performed through following databases; MEDLINE, Current Contents, Web of Science, and PubMed with the terms "endometrial cancer", "risk factors", "surgical treatment", "treatment", "chemotherapy", "radiation therapy", "targeted therapy". Furthermore, we searched the reference lists of articles identified by this search. We restricted our search to articles with human subjects only. International Federation of Gynecology and Obstetrics staging system of endometrial cancer are reviewed. Endometrial cancer has increased 21% in occurrence because 2008, and the death rate has actually increased more than 100% over the past twenty years. Adjuvant treatment is customized according to histology and stage. Numerous classifications are utilized to assess the threats of recurrence and to determine optimum postoperative management. the incorporation of Adjuvant therapy into treatment programs in endometrial cancer is an amazing area of investigation with the potential to enhance results. Outside of the advancement of a reliable screening test for endometrial cancer, transforming the disease to a chronic state and enhancing progression-free survival.**

Keywords: **Endometrial cancer, Numerous classifications, Risk Factors.**

1. INTRODUCTION

Endometrial cancer, is tumor coming from the endometrium, is the most common gynecological tumor in industrialized nations, and its prevalence is increasing [(1)]. As the disease is frequently symptomatic at an early stage, endometrial cancer is frequently identified at phase I. Historically, standard treatment consisted of hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymph node dissection followed by adjuvant treatment customized on the basis of last histology. Management of endometrial cancer has actually become more intricate during the past 5 - 10 years for a number of reasons: modifications in histological classification that impact surgical management, adjuvant treatments, and prognosis; modifications in the signs and modalities of lymphadenectomy; de-escalation of adjuvant treatment based upon information from randomized trials; and discrepancies in between the numerous classifications used to characterize recurrence risk factors [(1,2)].

The death rate per 100,000 population has actually increased more than 100% throughout the past 20 years and 8% because 2008. This is distressing given that overall death rates from cancer have actually decreased 1.6% each year in women, and these declines have actually corresponded because 2001 [(3,4)]. Ninety percent of females present with irregular uterine bleeding and almost 75% of ladies present with early stage disease. It is postulated that the increased death rate might be connected to an increasing life expectancy and coexisting medical comorbidities in these ladies. Women with a sophisticated stage diagnosed might have aggressive disease, denial of symptoms, genetic risk, confounding symptoms, or misdiagnosis [(4)].

In 2012, around 320 000 new cases of endometrial cancer were identified worldwide. Endometrial cancer is the 5th most common cancer in women (4.8 %of cancers in females), who have a cumulative risk of 1% of developing the disease by age 75 years [(1)]. It is the 14th cancer in terms of death (76 000 deaths); cumulative risk of death by age 75 years is 0.2 %

[1]. The highest occurrences in 2012 are estimated in the USA and Canada (19.1/100 000) and northern (12.9/ 100 000) and western Europe (15.6/ 100 000) [1,5]. Although endometrial cancer is conventionally believed to be a cancer of the postmenopausal period (ie, the 6th and seventh decades of life), 14% of cases are detected in premenopausal females, 5% of whom are younger than 40 years [6,7,8]. The increased occurrence of endometrial cancer in Europe and North America could be associated with a greater general frequency of weight problems and metabolic syndromes in these regions, in addition to the ageing of the population [9,10,11]. Projections show that the number of cases will increase to 42.13 per 100 000 in 2030 in the USA [10].

The aim of this review paper was to focus on discussing and overview the most important aspects of Endometrial cancer which is the most common gynecological cancer, and to specifically discuss the risk factors associated with this type of cancer, diagnostic procedures, and finally treatments approaches.

2. METHODOLOGY

We conducted a comprehensive search for articles published in English up to 2016. Search was performed through following databases; MEDLINE, Current Contents, Web of Science, and PubMed with the terms "endometrial cancer", "risk factors", "surgical treatment", "treatment", "chemotherapy", "radiation therapy", "targeted therapy". Furthermore, we searched the reference lists of articles identified by this search. We restricted our search to articles with human subjects only.

3. RESULTS

- **Risk factors associated with endometrial cancer:**

The epidemiology of endometrial cancer consists of ladies with genotypic and phenotypic risk. A recent prospective study reported that nearly 70% of females with early stage endometrial cancer were overweight [12]. This is greater than two times the portion of previous reports [13]. The Relative Risk (RR) for death increased with the body mass index (BMI). For ladies with endometrial cancer and BMIs of 24 - 30, the RR of death was 2.53, with BMIs of 35 - 40 the RR was 2.77, and with BMIs more than 40 the RR of death increased to 6.25 [14,15]. When compared with other cancers, women who endured endometrial cancer had the greatest rate of death. Women with endometrial cancer have other medical comorbidities that contribute to them dying from causes besides the cancer. Endometrial cancer survivors have unhealthy lifestyles that put them at risk for morbidity [16]. After medical diagnosis and treatment, survivors need to be used muiltibehavorial lifestyle interventions. Another study likewise showed that overweight endometrial cancer patients had a higher mortality from medical comorbidities. When compared with non-obese women [15], females with BMIs more than 40 had significantly much shorter survival and experienced more endometrial cancer-- unassociated deaths. A single institution research study of 442 ladies discovered BMI was likewise associated to tumor grade, race, and phase at diagnosis [17]. Reproductive, menstrual, and medical risk comorbidities can increase or reduce the risk of a lady having advancement of endometrial cancer [18]. Constant estrogen stimulation, albeit it exogenous or endogenous, can change the typical endometrial cycle. Anovulation results in constant unopposed estrogen stimulation because there is no corpus luteum to produce progesterone. Anovulation prevails throughout perimenopause. Obesity, normally more than 50 pounds over ideal body weight, can result in endogenous estrogen because of peripheral conversion of androstenedione into estrone. Ladies with BMIs more than 30 have 2 times to 3 times the risk of advancement of endometrial cancer. Data from observational research studies report that both symptomatic vaginal bleeding and postmenopausal status in females with endometrial polyps are associated with an increased risk of endometrial cancer [19]. Estrogen-producing tumors, unopposed estrogen treatment, tamoxifen, and cirrhosis also might lead to excess estrogen stimulation to the endometrium. Tamoxifen is an antiestrogen in breast tissue, it can have estrogenic activity in the endometrium [20].

- **Staging classifications, clinical and biological prognostic factors:**

The main objective of staging categories is to specify groups of patients with comparable outlooks to standardize management and allow comparisons of therapeutic methods. The 2009 International Federation of Gynecology and Obstetrics (FIGO) and the TNM categories are the most-adopted categories (**Table 1**) [21,22]. They are based upon surgical staging and include evaluation of the degree of myometrial intrusion and local and distant metastatic disease-- bypassing prognostic consider endometrial cancer [21,23]. Other prognostic factors not included in the FIGO or TNM categories have actually also been recognized: histological type and grade, the patient's age, tumor size, and lymphovascular space participation. Thus, risk stratifiation systems that aggregate these prognostic factors to define recurrence risk groups5

have actually been developed and are now used around the world to direct decision making and design scientific trials (**Table 2**) [24,25]. Although the core variables of these risk stratification systems are extremely similar, the combination of specifying variables varies. Outcomes of a 2014 study a simultaneous comparison of 5 risk stratification systems in the exact same mate recommended that the European Society for Medical Oncology customized system was the most accurate in the forecast of lymph node status and survival (25). Because of the limits of the conventional techniques utilized for histological classification of endometrial cancer subtypes, among the above research studies [24] recommended incorporation of molecular and genetic qualities into categories for much better appraisal of prognostic and predictive factors. Unique candidate prognostic markers, such as stathmin or L1 cell adhesion particle (L1CAM), and POLE mutations have been determined. Stathmin, a regulator of microtubule dynamics, is thought to be a possible predictive biomarker for resistance to taxanes [26]. L1CAM was found to be an unfavorable prognostic marker for type I, phase I endometrial cancer in a large study (of 1021 patients) and exceeded risk stratification systems [27]. These outcomes were verified in a combined analysis of the Post-Operative Radiation Therapy in Endometrial Carcinoma (PORTEC) 1 and PORTEC 2 trials; the analysis also revealed L1CAM to be a strong predictor of distant regression [28].

Table 1: FIGO and TNM classification of endometrial cancer,

	FIGO staging*	**TNM category**
Primary tumour cannot be assessed	··	TX
No evidence of primary tumour	··	T0
Carcinoma in situ	··	Tis†
Tumour confined to the corpus uteri	Stage I	T1
Tumour limited to endometrium or invades less than 50% of the myometrium	Stage IA	T1a
Tumour invades 50% or more of the myometrium	Stage IB	T1b
Tumour invades cervical stroma but does not extend beyond uterus	Stage II	T2
Tumour with local or regional extension	Stage III	T3 or N1–2, or both
Tumour involves serosa or adnexa, or both	Stage IIIA	T3a
Vaginal involvement or parametrial involvement	Stage IIIB	T3b
Regional lymph node metastasis	Stage IIIC	
Regional pelvic lymph node metastasis	Stage IIIC1	N1
Regional para-aortic lymph node metastasis with or without pelvic lymph node metastasis	Stage IIIC2	N2
Tumour invades bladder or bowel mucosa, or distant metastatic disease present (or any combination thereof)	Stage IV	
Tumour invades bladder or bowel, or both	Stage IVA	T4
Distant metastatic disease (includes inguinal lymph node, intraperitoneal disease, lung, bone, or liver)	Stage IVB	M1

TNM classification: NX (regional lymph nodes cannot be assessed), N0 (no regional lymph node metastasis), and M0 (no distant metastasis). FIGO=International Federation of Gynecology and Obstetrics. *Either G1, G2, or G3. †FIGO does not include stage 0 (Tis) in its classification.

Table 2: Classification of Endometrial Cancer

Type I	**Type II**	**Familial**
Low-grade	High-grade	Lynch
Minimal myometrial invasion	Deep myometrial invasion	
Arising in a background of hyperplasia	Serous or clear-cell	
Perimenopausal		
Estrogen-related		
Younger age		
Obesity		

➢ **Diagnosis of Endometrial cancer:**

Irregular uterine bleeding including postmenopausal bleeding, menorrhagia, or metrorrhagia are the most common presenting signs for ladies with endometrial hyperplasia or carcinoma. Atypical glandular cells on cytologic screening should be examined with colposcopy and endocervical curettage and an endometrial biopsy in females older than age 35 years or those with risk factors for endometrial cancer [29,30]. Endometrial tasting ought to be suggested in women older than 40 years with irregular bleeding or in more youthful ladies with risk factors for disease. Due to the fact that of the high occurrence of a coexistent cancer, a dilation and curettage (D&C) should be performed if complicated hyperplasia with atypia is spotted. Hysteroscopy is typically scheduled for those women who continue to have symptoms that cannot be described by workplace biopsy. Hysteroscopy is much better than curettage at detecting polyps and submucosal leiomyomas. Based upon information from observational studies, both symptomatic vaginal bleeding and postmenopausal status in females with endometrial polyps are associated with an increased risk of endometrial cancer [19]. Whereas sonohysterography also can identify these sores, a tissue medical diagnosis may be required depending upon the clinical context (**Figure 1**). Making use of hysteroscopy for examination of abnormal bleeding is common. When endometrial cancer is identified after hysteroscopy sampling of the peritoneal fluid during standard cancer staging, surgical treatment has in some cases led to favorable cytologic findings. The scientific significance of malignant cytology and the potential for tumor dissemination after hysteroscopic after medical diagnosis of endometrial cancer is uncertain [31].

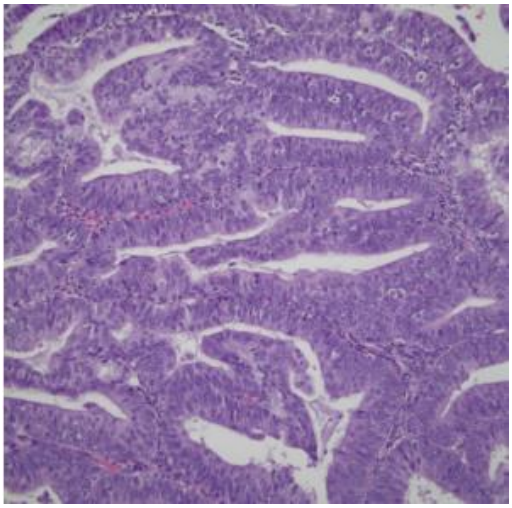

Figure 1: Endometroid adenocarcinoma

➢ **Treatment option for Endometrial cancer:**

Surgical intervention:

Endometrial cancer is at first staged and dealt with at surgical treatment. Standard treatment for this cancer in the United States includes removal of the uterus, cervix, both fallopian tubes and ovaries, along with selective pelvic and para-aortic lymphadenectomy. Details concerning the requirement for lymph node dissection in all cases is hard to understand with data supporting both views. It appears that it is reasonable to figure out the risk of nodal transition in order to assign patients to a low risk group and a high risk group. A recent publication reporting the risk for lymph node metastasis in high versus low risk patients from a secondary analysis of Gynecologic Oncology Group (GOG) study LAP2 shows just 0.8% of patients in the low risk group had nodal participation [32]. Hence, unnecessary lymphadenectomy might be avoidable in those patients with very low risk for nodal disease. Based upon information from GOG study 33, the two factors crucial in determining lymph node involvement are depth of tumor intrusion and tumor grade [33]. Previous research studies taking a look at patients with early stage disease have shown greater reoccurrence rates in patients with positive lymph nodes in addition to decreased survival rates [34,35]. 2 large prospective studies that analyzed the value of lymph node dissection found no survival difference between groups who did or did not undergo lymphadenectomy. Yet, there were limitations to both of these studies, particularly the addition of postoperative treatment and the lack of total pelvic and paraaortic lymph node dissection [36,37]. The long-lasting risks of lymph node dissection are rather uncommon [38]. Reasonably current data from the LAP2 trial has demonstrated the safe use of minimally invasive methods for lymph node dissection when compared to an open procedure [39]. Although the intraoperative complication rates were similar in between these two groups, this study did not particularly take a look at the complication rates of lymph node dissection. A

publication from the Mayo Clinic proposes the identification of a low risk subset of patients where lymph node dissection can be avoided [40]. No patients in this group had favorable lymph nodes, thus showing and validating the belief that lymph node dissection may be best carried out in patients with a high risk for nodal involvement. For females who are not surgical prospects, primary radiation therapy (RT) may be recommended instead of surgery. As an alternative for younger females wishing to protect fertility, progestin-containing intrauterine devices (IUDs) have actually been utilized with affordable security and efficacy [41,42], though this has actually mainly been performed in patients with grade 1 disease. Nevertheless, one case of grade 2 has been reported to be successfully dealt with [41].

Adjuvant therapy& Chemotherapy:

For those patients who have actually undergone a suitable staging and treatment surgical treatment, adjuvant RT (vaginal brachytherapy or external beam), chemotherapy or hormonal therapy might be suggested relying on risk factors. Patients are categorized based upon risk stratification in the post-operative duration [43]. Low-intermediate-risk and low patients might not require post-surgical therapy; however, molecular risk factors such as p53 anomalies, and so on if known, might affect this choice. Offered the potential side effects of adjuvant treatment, it is very important to compare patients who would take advantage of adjuvant therapy and those who would be better served simply by close clinical subsequent.

Those of high-intermediate-risk require post-surgical treatment with RT to minimize local reoccurrence based upon the fact that 75% of recurrences remain in the pelvis. Presently, there is no reputable treatment protocol for patients with advanced-stage disease, although this is the topic of clinical trials. Patients at high risk require adjuvant treatment, which is usually RT for high risk cases restricted to the uterus and chemotherapy for cases with extrauterine disease. Big prospective clinical trials have actually demonstrated that post-operative pelvic radiation treatment does decrease local recurrences, however has no overall influence on survival [43,44].

Many clinicians had concerns relating to the side effects of entire pelvic radiation in treating patients with early stage endometrial cancer. Current evidence from PORTEC-2 demonstrates that making use of vaginal brachytherapy is no worse that entire pelvic radiation treatment, and as a result of this trial lots of centers within the United States have moved to making use of vaginal brachytherapy for their patients in whom adjuvant radiation treatment is required [45]. Long-lasting subsequent research studies for PORTEC-1 and PORTEC-2 have actually demonstrated more urinary and bowel dysfunction for patients treated with whole pelvic radiation therapy (PORTEC-1) and, as anticipated, patients who received vaginal brachytherapy showed less adverse results than those who received pelvic radiation (PORTEC-2) [46,47].

Weight problems is clearly a risk factor for the development of endometrial cancer, however the mechanisms by which this occurs are not well comprehended [34]. While production of estrone from the fat with local conversion to estradiol in the endometrium is one hypothesis, current publications indicate a genetic link in between obesity and endometrial cancer. An association between single nucleotide polymorphisms in genes related to obesity and endometrial cancer was just recently made [48,49]. Much info remains to be understood about the relationship between weight problems and endometrial cancer, and support for these efforts are being recognized by the National Cancer Institute (NCI) and other financing agencies, as is reflected by the NCI's recent request for applications directly related to obesity.

Chemotherapy is the treatment of choice for metastatic disease. The choice of the routine has actually progressed over the past years. The most active agents are anthracyclines, platinum compounds and taxanes. As single representatives, these drugs lead to a response rate greater than 20%. Single representative chemotherapy is an alternative for patients who are most likely to have unacceptable adverse effects with multiple representatives. For the majority of patients, several agents are utilized. Response rates for triple therapy with paclitaxel, cisplatin and doxorubicin were 57% in GOG 177; nevertheless, adverse effects were prominent [50]. Stage II trials indicate that the double combination of cisplatin and paclitaxel lead to a reasonably high rate of reaction, and this program appears to be much better tolerated [51,52].

4. CONCLUSION

International Federation of Gynecology and Obstetrics staging system of endometrial cancer are reviewed. Endometrial cancer has increased 21% in occurrence because 2008, and the death rate has actually increased more than 100% over the past twenty years. Adjuvant treatment is customized according to histology and stage. Numerous classifications are utilized to assess the threats of recurrence and to determine optimum postoperative management. the incorporation of Adjuvant therapy into treatment programs in endometrial cancer is an amazing area of investigation with the potential to enhance results. Outside of the advancement of a reliable screening test for endometrial cancer, transforming the disease to a chronic state and enhancing progression-free survival.

REFERENCES

[1] Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015; 136: E359–86.

[2] Querleu D, Planchamp F, Narducci F, et al, and the Institut National du Cancer, and the Societe Francaise d'Oncologie Gynecologique. Clinical practice guidelines for the management of patients with endometrial cancer in France: recommendations of the Institut National du Cancer and the Société Française d'Oncologie Gynécologique. Int J Gynecol Cancer 2011; 21: 945–50

[3] Siegel R, Naishadham J, Jemal A. Cancer statistics 2012. CA Cancer J Clin 2012;62:10 –29.

[4] Sorosky JI. Endometrial cancer. Obstet Gynecol 2008;111: 436 – 47.

[5] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65: 5–29.

[6] Evans-Metcalf ER, Brooks SE, Reale FR, Baker SP. Profi le of women 45 years of age and younger with endometrial cancer. Obstet Gynecol 1998; 91: 349–54.

[7] Lee TS, Jung JY, Kim JW, et al. Feasibility of ovarian preservation in patients with early stage endometrial carcinoma. Gynecol Oncol 2007; 104: 52–57.

[8] Duska LR, Garrett A, Rueda BR, Haas J, Chang Y, Fuller AF. Endometrial cancer in women 40 years old or younger. Gynecol Oncol 2001; 83: 388–93.

[9] Lacey JV Jr, Chia VM, Rush BB, et al. Incidence rates of endometrial hyperplasia, endometrial cancer and hysterectomy from 1980 to 2003 within a large prepaid health plan. Int J Cancer 2012; 131: 1921–29.

[10] Sheikh MA, Althouse AD, Freese KE, et al. USA endometrial cancer projections to 2030: should we be concerned? Future Oncol 2014; 10: 2561–68.

[11] Trabert B, Wentzensen N, Felix AS, Yang HP, Sherman ME, Brinton LA. Metabolic syndrome and risk of endometrial cancer in the United States: a study in the SEER-medicare linked database. Cancer Epidemiol Biomarkers Prev 2015; 24: 261–67

[12] Courneya KS, Karvinen KH, Campbell KL, Pearcey RG, Dundas G, Capstick V, et al. Associations among exercise, body weight, and quality of life in a population-based sample of endometrial cancer survivors. Gynecol Oncol 2005;97: 422–30.

[13] Anderson B, Connor JP, Andrews JI, Davis CS, Buller RE, Sorosky JI, et al. Obesity and prognosis in endometrial cancer. Am J Obstet Gynecol 1996;174:1171–78.

[14] 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: 1625–38.

[15] von Gruenigen VE, Tian C, Frasure H, Waggoner S, Keys H, Barakat RR. Treatment effects, disease recurrence, and survival in obese women with early endometrial carcinoma: a Gynecologic Oncology Group study. Cancer 2006;107: 2786 –91.

[16] von Gruenigen VE, Waggoner SE, Frasure HE, Kavanagh MB, Janata JW, Rose PG, et al. Lifestyle challenges in endometrial cancer survivorship. Obstet Gynecol 2011;117:93–100.

[17] Temkin SM, Pezzullo JC, Hellmann M, Lee YC, Abulafia O. Is body mass index an independent risk factor of survival among patients with endometrial cancer? Am J Clin Oncol 2007;30: 8 –14.

[18] 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;167:1317–25.

[19] Lee SC, Kaunitz AM, Sanchez-Ramos L, Rhatigan RM. The oncogenic potential of endometrial polyps: A systemic review and meta-analysis. Obstet Gynecol 2010;116:1197–205.

[20] Fisher B, Costantino JP, Wickerham DL, Redmond CK, Kavanah M, Cronin M, et al. Tamoxifen for prevention of breast cancer: report of the National Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90:1371– 88.

[21] Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet 2009; 105: 103–04.

[22] Union internationale contre le cancer (UICC). TNM: Classifi cation des tumeurs malignes, 7th edn. New York, NY: Wiley-Blackwell, 2009.

[23] Barlin JN, Zhou Q, St Clair CM, et al. Classifi cation and regression tree (CART) analysis of endometrial carcinoma: seeing the forest for the trees. Gynecol Oncol 2013; 130: 452–56.

[24] 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: 1404–11.

[25] Keys HM, Roberts JA, Brunetto VL, et al, and the Gynecologic Oncology Group. 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: 744–51.

[26] Werner HM, Trovik J, Halle MK, et al. Stathmin protein level, a potential predictive marker for taxane treatment response in endometrial cancer. PLoS One 2014; 9: e90141.

[27] Zeimet AG, Reimer D, Huszar M, et al. L1CAM in early-stage type I endometrial cancer: results of a large multicenter evaluation. J Natl Cancer Inst 2013; 105: 1142–50.

[28] Bosse T, Nout RA, Stelloo E, et al. L1 cell adhesion molecule is a strong predictor for distant recurrence and overall survival in early stage endometrial cancer: pooled PORTEC trial results. Eur J Cancer 2014; 50: 2602–10.

[29] Sharpless KE, Schnatz PF, Mandavilli S, Greene JF, Sorosky JI. Dysplasia associated with atypical glandular cells on cervical cytology. Obstet Gynecol 2005;105:494 –500.

[30] Schnatz PF, Guile M, O'Sullivan DM, Sorosky JI. Clinical significance of atypical glandular cells on cervical cytology. Obstet Gynecol 2006;107:701– 8.

[31] Guralp O, Kushner DM. Iatrogenic transtubal spill of endometrial cancer: risk of myth. Ach Gynecol Obstet Gynecol 2011;284:1209 –21.

[32] Milam MR, et al. Nodal metastasis risk in endometrioid endometrial cancer. Obstet Gynecol. 2012;119(2 Pt 1):286–92.

[33] Creasman WT, et al. Surgical pathologic spread patterns of endometrial cancer. A Gynecologic Oncology Group Study. Cancer. 1987;60(8 Suppl):2035–41.

[34] Morrow CP, et al. Relationship between surgical-pathological risk factors and outcome in clinical stage I and II carcinoma of the endometrium: a Gynecologic Oncology Group study. Gynecol Oncol. 1991;40(1):55–65.

[35] Lurain JR, et al. Prognostic factors associated with recurrence in clinical stage I adenocarcinoma of the endometrium. Obstet Gynecol. 1991;78(1):63–9.

[36] Kitchener H, et al. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet. 2009;373(9658):125–36.

[37] Benedetti Panici P, et al. Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. J Natl Cancer Inst. 2008;100(23):1707–16.

[38] Orr JW, Jr., et al. Surgical staging of uterine cancer: an analysis of perioperative morbidity. Gynecol Oncol. 1991;42(3):209–16.

[39] Walker JL, 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.

[40] Mariani A, et al. Prospective assessment of lymphatic dissemination in endometrial cancer: a paradigm shift in surgical staging. Gynecol Oncol. 2008;109(1):11–8.

[41] Brown AJ, et al. Progestin intrauterine device in an adolescent with grade 2 endometrial cancer. Obstet Gynecol. 2012;119(2 Pt 2):423–6.

[42] Leslie KK, Thiel KW, Yang S. Endometrial cancer: potential treatment and prevention with progestin-containing intrauterine devices. Obstet Gynecol. 2012;119(2 Pt 2):419–20.

[43] Keys HM, et al. A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. Gynecol Oncol. 2004;92(3):744–51.

[44] Creutzberg CL, et al. Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. Lancet. 2000;355(9213):1404–11.

[45] Nout RA, et al. Vaginal brachytherapy versus pelvic external beam radiotherapy for patients with endometrial cancer of high-intermediate risk (PORTEC-2): an open-label, non-inferiority, randomised trial. Lancet. 2010;375(9717):816–23.

[46] Nout RA, et al. Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. J Clin Oncol. 2011;29(13):1692–700.

[47] Nout RA, et al. Five-year quality of life of endometrial cancer patients treated in the randomised Post Operative Radiation Therapy in Endometrial Cancer (PORTEC-2) trial and comparison with norm data. Eur J Cancer. 2011

[48] Delahanty RJ, et al. Association of obesity-related genetic variants with endometrial cancer risk: a report from the Shanghai Endometrial Cancer Genetics Study. Am J Epidemiol. 2011;174(10):1115–26.

[49] Chen X, et al. Genetic polymorphisms in obesity-related genes and endometrial cancer risk. Cancer. 2011

[50] Fleming GF, 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.

[51] Hoskins PJ, et al. Paclitaxel and carboplatin, alone or with irradiation, in advanced or recurrent endometrial cancer: a phase II study. J Clin Oncol. 2001;19(20):4048–53.

[52] Sorbe B, et al. Treatment of primary advanced and recurrent endometrial carcinoma with a combination of carboplatin and paclitaxel-long-term follow-up. Int J Gynecol Cancer. 2008;18(4):803–8.