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ENDOMETRIAL CANCER. A REVIEW AND EVALUATION OF RISK FACTORS.

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Abstract: Uterine body cancer represents the uncontrolled and chaotic growth of some abnormal cells from the womb lining, being thus included in the category of gynaecologic cancers. The main risk factors for endometrial cancer are: ageing, nutritional imbalances that lead to obesity, diabetes, high blood pressure, nulliparity. This article is made up of a retrospective study for incidence of the endometrial cancer. We had reviewed the literature and created evidence-based practice recommendations for diagnosis and treatment. This review examines: risk factors, diagnostic and metastatic evaluation.

INTRODUCTION

Anatomy: The endometrium is the inner lining of the uterus and has both functional and basal layers. The functional layer is hormonally sensitive and is shed in a cyclical pattern during menstruation in reproductive-age women. Both estrogen and progesterone are necessary to maintain a normal endometrial lining. However, factors that lead to an excess of estrogen, including obesity and anovulation, lead to an increase in the deposition of the endometrial lining (Jayaraman M. et al., 2017). These changes may lead to endometrial hyperplasia, and, in some cases, endometrial cancer. Whatever the cause, a thickened lining will lead to sloughing of the endometrial tissue through the endometrial canal and into the vagina. As a result, heavy menstrual bleeding or bleeding after menopause are often the initial signs of endometrial cancer. This symptom tends to happen early in the disease course, allowing for identification of the disease at an early stage for most women (Ferlay J. et al., 2013).

Endometrial cancer is the sixth most frequent cancer in women worldwide, with about 290,000 new cases and 74,000 deaths in 2008 (Andreano A. et al., 2014). It is the most common gynaecological malignancy in western countries with 49,560 estimated new cases in 2013 in the USA and 98,900 in 2012 in Europe (Ferlay J. et al., 2013); (Sala E. et al., 2013). Well-known negative prognostic factors are high tumour grade, deep myometrial invasion (≥50% myometrial thickness), lymphovascular space invasion, non-endometrioid histology, and cervical stroma involvement (Ferlay J. et al., 2013). Among those, the most important single morphological prognostic feature is depth of myometrial invasion with a one-half cut-off, which divides the current stage I of the International Federation of Gynecology and Obstetrics (FIGO) staging system into Ia and Ib (Kisu I. et al., 2013); (Sala E. et al., 2013). The purpose of this document is to review the risks and benefits of current treatment options and optimize treatment for women with endometrial cancer.

Epidemiology

In the United States, endometrial cancer will be diagnosed in an estimated 52,630 women in 2014,with 8590 succumbing to their disease. Most endometrial cancers are diagnosed at an early stage (75%), and the reported survival rate is 75% (Burke WM. et al., 2014). The mean age of diagnosis in the United States is 60 years. Caucasian women have a 2.88% lifetime risk of developing uterine cancer compared with a 1.69% risk for African - American women. African-American women are more likely to have non-endometrioid, high-grade tumors and a more advanced stage of disease at the time of diagnosis compared with Caucasian women who have similar demographics (Siegel R. et al., 2013). Endometrial cancer usually appears at elderly women, the peak frequency being at ages of 55-65 years old, but it can be met at the young woman (<40 years old). In Romania, endometrial cancer is on the fourth place, among gynaecologic cancers, and seventh place, as a number of deaths through cancer. Endometrial cancer is a disease characteristic for the postmenopausal period, the majority of the female patients of the studied lot, having the age between 51-60 years old (Valu MV, Toma O., 2017). Prognosis depends on patient age, histological type, grade, tumour size, depth of myometrial invasion, the presence of cervical stroma invasion, and lymph-node metastases (Epstein E. et al., 2014). Most women are diagnosed at stage I, in which prognosis is generally good, and the 5-year survival is 88% (Antonsen SL. et al., 2013); (Mascilini F. et al., 2013). The prognosis is worse for women with high-risk cancer (i.e. deep myometrial invasion, cervical stroma invasion, or high-grade disease see below for an explanation), as these women are at increased risk of lymph-node metastases (Thomsen HS. et al., 2013). Most cases of endometrial cancer cannot be prevented, but there are some things that may lower your risk of

developing this disease. One way to lower endometrial cancer risk is to do what you can to change your risk factors when ever possible. For example, women who are overweight or obese have up to 3½ times the risk of getting endometrial cancer compared with women at a healthy weight. Getting to and maintaining a healthy weight is one way to lower the risk of this cancer. Studies have also linked higher levels of physical activity to lower risks of endometrial cancer, so engaging in regular physical activity (exercise) may also be a way to help lower endometrial cancer risk (Bendifallah S. et al., 2015); (Creutzberg CL. et al., 2015). An active lifestyle can help you stay at a healthy weight, as well as lower the risk of high blood pressure and diabetes (other risk factors for endometrial cancer). Estrogen to treat the symptoms of menopause is available in many different forms like pills, skin patches, shots, creams, and vaginal rings. Progestins (progesterone-like drugs) can reduce the risk of endometrial cancer in women taking estrogen therapy, but this combination increases the risk of breast cancer. Getting proper treatment of pre-cancerous disorders of the endometrium is another way to lower the risk of endometrial cancer. Most endometrial cancers develop over a period of years (Creutzberg CL. et al., 2015). Many are known to follow and possibly start from less serious abnormalities of the endometrium called endometrial hyperplasia. Some cases of hyperplasia will go away without treatment, but it sometimes needs to be treated with hormones or even surgery. Treatment with progestins and a dilation and curettage (D&C) or hysterectomy can prevent hyperplasia from becoming cancerous. Abnormal vaginal bleeding is the most common symptom of endometrial pre-cancers and cancers, and it needs to be reported and evaluated right away. Women with hereditary nonpolyposis colon cancer (HNPCC or Lynch syndrome) have a very high risk of endometrial cancer. A woman with HNPCC may choose to have her uterus removed (a hysterectomy) after she has finished having children to prevent endometrial cancer. One study found that none of 61 women with HNPCC who had prophylactic (preventive) hysterectomies was later found to have endometrial cancer, while 1/3 of the women who didn't have the surgery were diagnosed with endometrial cancer over the next 7 years (Jayaraman M. et al., 2017).

Risk factors

We do not yet know exactly what causes most cases of endometrial cancer, but we do know certain risk factors, particularly hormone imbalance, for this type of cancer. A great deal of research is going on to learn more about the disease. We know that most endometrial cancer cells contain estrogen and/or progesterone receptors on their surfaces. Somehow, interaction of these receptors with their hormones leads to increased growth of the endometrium. This can mark the beginning of cancer. The increased growth can become more and more abnormal until it develops into a cancer. (Jayaraman M. et al., 2017). Prolonged unopposed estrogen exposure is associated with most type I endometrial cancers. Estrogen replacement therapy prescribed to control menopausal symptoms increases the risk of developing endometrial cancer by 2- to 20-fold, with an increasing risk correlating with the duration of use. Concomitant administration of progestins continuously or intermittently (10 to 15 days/month) significantly reduces this increased risk of cancer (Busch EL. et al., 2017). Exposure to unopposed endogenous estrogen, as occurs in chronic anovulation (polycystic ovary syndrome), with estrogen-producing tumors, and with excessive peripheral conversion of androgens to estrone in adipose tissue, is also associated with an increased risk for developing endometrial hyperplasia and cancer. Tamoxifen, a selective estrogen receptor modulator, acts as an estrogen antagonist in breast tissues and an agonist in bone and endometrial tissues. Tamoxifen use is associated with a 6- to 8-fold increase in the incidence of endometrial cancer (Guinney J. et al., 2015); (Mutter GL. et al., 2014); (Zaino RJ. et al., 2014). The obesity epidemic in the Romania may have a profound impact on the incidence of endometrial cancer seen this country. The profound increased incidence of endometrial cancer associated with obesity may be explained by higher endogenous estrogen production via aromatization in adipose tissues. Additionally, premenopausal obese women are more likely to suffer from chronic anovulation (Mutter GL. et al., 2014). Diabetes mellitus is associated with an increased risk for endometrial cancer that may be related to concurrent obesity, although an independent association between diabetes and endometrial cancer has been reported. Hypertension has been epidemiologically associated with an increased risk of endometrial cancer, but whether hypertension represents an independent risk factor or the association is confounded by the presence of medical comorbidities, such as diabetes and obesity, is unclear (Zaino RJ. et al., 2014). Age also represents an important risk factor for developing endometrial cancer. Most women are diagnosed after menopause, with only 15% diagnosed before the age of 50 years and only 5% before 40 years of age. Younger women who develop endometrial cancer are more likely to be obese and nulliparous and have well-differentiated endometrioid histology and lower-stage disease than older women (Guinney J. et al., 2015). Reproductive characteristics associated with increased risk of endometrial cancer include nulliparity, infertility, early age of menarche, and late age of menopause (Allot EH. et al., 2016); (Cheang MC. et al., 2015). Importantly, the use of combination oral contraceptive pills, depot medroxyprogesterone acetate, and progesterone secreting intra-uterine devices reduces the risk of developing endometrial cancer. Smoking has also been associated with a reduced risk for endometrial cancer, especially in postmenopausal women (Allot EH. et al., 2016). Genetic disorders can also cause endometrial cancer. Overall, hereditary causes contribute to 2–10% of endometrial cancer cases. Lynch syndrome, an autosomal dominant genetic disorder that mainly causes colorectal cancer, also causes endometrial cancer, especially before menopause. Women with Lynch syndrome have a 40–60% risk of developing

endometrial cancer, higher than their risk of developing colorectal (bowel) or ovarian cancer (Jayaraman M. et al., 2017). Ovarian and endometrial cancer develop simultaneously in 20% of people. Endometrial cancer nearly always develops before colon cancer, on average, 11 years before. Carcinogenesis in Lynch syndrome comes from a mutation in MLH1 and/or MLH2: genes that participate in the process of mismatch repair, which allows a cell to correct mistakes in the DNA (Guinney J. et al., 2015). Other genes mutated in Lynch syndrome include MSH2, MSH6, and PMS2, which are also mismatch repair genes. Women with Lynch syndrome represent 2–3% of endometrial cancer cases; some sources place this as high as 5%. Depending on the gene mutation, women with Lynch syndrome have different risks of endometrial cancer. With MLH1 mutations, the risk is 54%; with MSH2, 21%; and with MSH6, 16%. Women with a family history of endometrial cancer are at higher risk. Two genes most commonly associated with some other women's cancers, BRCA1 and BRCA2, do not cause endometrial cancer (Mutter GL. et al., 2014). There is an apparent link with these genes but it is attributable to the use of tamoxifen, a drug that itself can cause endometrial cancer, in breast and ovarian cancers. The inherited genetic condition Cowden syndrome can also cause endometrial cancer. Women with this disorder have a 5–10% lifetime risk of developing endometrial cancer, compared to the 2–3% risk for unaffected women (Allot EH. et al., 2016). The International Federation of Gynecology and Obstetrics (FIGO) classification system is most often used to stage endometrial carcinoma (Table 1), and the staging remains surgical as the treatment is most often surgical.

Table 1

FIGO 2010 classification of carcinoma of the endometrium.
IA. Tumour confined to the uterus, no or <50% myometrial invasion
IB. Tumour confined to the uterus, 50% myometrial invasion
II. Cervical stromal invasion, but not beyond the uterus
IIIA. Tumour invades serosa or adnexa
IIIB. Vaginal, parametrial involvement, or both
IIIC1. Pelvic-lymph node involvement
IIIC2. Para-aortic lymph-node involvement
IVA. Tumour invasion of bladder, bowel mucosa, or both
IVB. Distant metastases, including abdominal metastases, inguinal lymph nodes, or both

FIGO, International Federation of Gynecology and Obstetrics (2010).

Clinical presentation and diagnostic assessment

Abnormal uterine bleeding - sometimes associated with vaginal discharge and pyometra is the most frequent symptom of endometrial cancer and is noted in about 90% of patients (usually during menopause). Patients with advanced disease might have symptoms similar to those of advanced ovarian cancer, such as abdominal or pelvic pain and abdominal distension (Ferlay J. et al., 2015). Disease can easily be diagnosed on the basis of office-based pipelle sampling or other techniques. The histological information provided by endometrial biopsy is sufficient for preoperative assessment and planning. However, pipelle sampling can be infeasible in some postmenopausal women because of cervical stenosis (Siegel RL. et al., 2015); (Trabert B. et al., 2015); (Hussein YR. et al., 2015). When histological findings from an endometrial biopsy are insufficient to confirm diagnosis, cervical dilation and curettage is recommended, although this investigation necessitates anaesthesia and has been associated with disease underestimation (Ferlay J. et al., 2015). A biopsy under hysteroscopy remains the gold standard for diagnosis of endometrial cancer and yields higher accuracy than does blind dilation and curettage. Results of some studies suggested a higher incidence of malignant peritoneal cytology at the time of hysterectomy in patients who underwent previous hysteroscopy than in those who did not, but no evidence supports an association between diagnostic hysteroscopy and worse prognosis (Hussein YR. et al., 2015). Thus, the standard strategy for investigation of abnormal uterine bleeding is pelvic ultrasonography with an endometrial biopsy in cases of increased endometrial thickness and a hysteroscopy when diagnosis is uncertain. A review of 13 studies showed that, in menopausal women, an endometrial thickness cutoff of 5 mm on ultrasonography had sensitivity of 90% and specificity of 54% compared with 98% and 35%, respectively, when the cutoff was reduced to 3 mm (Siegel RL. et al., 2015).

Treatment and survival

Uterine cancers are usually treated with surgery, radiation therapy, hormone therapy, and/or chemotherapy, depending on stage of disease and histologic type (Jagsi R. et al., 2014). Surgery alone, consisting of hysterectomy (often along with bilateral salpingo-oopherectomy), is used to treat 72% of patients with early-stage disease. Approximately 22% of early-stage disease is high-risk disease and is treated with radiation either alone, or in combination with chemotherapy, in addition to surgery. The majority (64%) of women with advanced disease undergo surgery followed by radiation therapy and/or chemotherapy. Clinical trials are currently assessing the most appropriate regimen of radiation therapy and chemotherapy for women with metastatic or recurrent uterine cancer (James JA. et al., 2015). Most cancers of the uterine corpus (68%) are diagnosed at an early stage, usually because of postmenopausal bleeding (Todo Y. et al., 2015). The 1-year and 5-year relative survival rates for patients with cancer of the uterine corpus are 92.1% and 81.5%, respectively. The 5-year survival rate is 95.3% for localized disease, 67.5% for regional disease, and 16.9% for distant-stage disease. The overall 5-year survival for white women (84%) is 23% higher than that for black women (61%) (Deura I. et al., 2015); (Biglia N. et al., 2015); (Rowlands IJ et al., 2015). Higher body weight adversely affects endometrial cancer survival, whereas physical activity is associated with improved survival (Hopp EE. et al., 2015); (Hareyama H. et al., 2015). Any hysterectomy causes infertility. Bilateral oophorectomy will cause menopause in premenopausal women, which can lead to symptoms such as hot flashes, night sweats, vaginal dryness, and osteoporosis (Ferrandina G. et al., 2014). Long-term side effects of radiation therapy for uterine cancer can include bladder and bowel dysfunction, as well as vaginal dryness and stenosis. Sexual problems are commonly reported among uterine cancer survivors (Herling SF. et al., 2015); (Beesley VL. et al., 2015). Pelvic lymphadenectomy can lead to lower extremity lymphedema, particularly for women who also receive radiation therapy (Bae HS. et al., 2016); (Mitra D. et al., 2016); (Mendivil AA. et al., 2016). The “gold standard” treatment for endometrial cancer is completely staged surgery, followed by radiation or chemotherapy, based on the final pathological surgical stage and requirements. In the primary treatment of endometrial cancers, hormones are rarely taken into consideration after primary surgery (Bendifallah S. et al., 2015); (Creutzberg CL. et al., 2015). Primary treatment with hormones to preserve fertility in younger women with endometrial cancer is an attractive option, and many successful cases have been reported, although the majority of them finally received definite therapy, including total hysterectomy (Beesley VL. et al., 2015). The role of hormone therapy is often delayed in recurrent disease; response rates to progestins and tamoxifen or aromatase inhibitors in advanced/recurrent endometrial cancers are approximately 15-20% and nearly ≤10%, respectively (Creutzberg CL. et al., 2015).

Surgery: Total hysterectomy and removal of both tubes and ovaries is the standard treatment for apparent stage I endometrial cancer and is effective in most cases. Alternatives to primary hysterectomy in women who want to preserve their fertility have been comprehensively reviewed. Hysterectomy and adnexectomy can be done with minimally invasive techniques (laparoscopy or robot-assisted surgery), vaginally, or laparotomically (Bradford LS. et al., 2015). The safety of laparoscopy has been shown in randomized clinical trials and is associated with shorter hospital stays and fewer postoperative complications than laparotomy. Survival rates seem similar, which should be confirmed by completed trials (eg, NCT00096408). Laparoscopic or robotic approaches should be avoided in cases of bulky uterine malignant disease that might necessite morcellation, because morcellation can lead to tumour spillage, increasing local or peritoneal recurrence and thereby affecting survival (Oza A. et al., 2015); (Slomovitz BM. et al., 2015). Although simple total hysterectomy is sufficient for most women, radical hysterectomy is sometimes done in cases of gross cervical invasion or when uncertainty exists about whether the primary tumour is endocervical or endometrial in origin. Surgical staging for endometrial cancer includes careful assessment of the peritoneal surfaces (Matulonis U. et al., 2015). Omental and peritoneal biopsies are commonly done in high-risk disease. Estimated cumulative risk of endometrial cancer is 0-96%; the corresponding mortality risk is 0-23% and mortality-to-incidence ratio is 0-24 - lower than that of breast cancer (0-32), ovarian cancer (0-63), and uterine cervical cancer (0-55). Most endometrial cancers (75%) are diagnosed at an early stage (FIGO stages I or II): 5 year overall survival ranges from 74% to 91%; for FIGO stage III, 5 year overall survival is 57–66%, and for FIGO stage IV disease is 20–26%, 5 year disease survival is estimated at 90% in patients without lymph node metastasis, 60–70% in those with pelvic lymph node metastasis, and 30–40% in those with paraaortic lymph node metastasis (Howitt BE. et al., 2015); (Moir-Meyer GL. et al., 2015). However, a substantial proportion of patients with endometrial cancer die from other health conditions as these patients often have several comorbidities (Coleman RL. et al., 2015). Survival is dependent on other predictive factors, such as the tumour grade, age, comorbidities, tumour diameter, American Society of Anesthesiologists score, lymphovascular space involvement, and postoperative complications at 30 days (Slomovitz BM. et al., 2015). Among the various nomograms predicting survival, two have been validated externally. The first to be published consists of five simple criteria (age at diagnosis, negative lymph nodes, FIGO stage, final histological grade, and histological subtype). The second was validated in randomly assigned patients from the PORTEC 1 and PORTEC 2 trials and showed that age, tumour grade, and lymphovascular space involvement were highly predictive for all outcomes (Bradford LS. et al., 2015).

CONCLUSIONS

We searched Pubmed and Embase for studies on body mass index and the risk of endometrial cancer, published from 2013 to 2017. Data were independently extracted and analyzed using random or fixed effects meta-analysis depending on the degree of heterogeneity. The findings from this meta-analysis strongly support that the conditions of EBW (excess body weight), overweight, and obesity are all associated with an increased risk of endometrial cancer. Also, the strength of the association increases with increasing BMI (body mass index - ≥30kg m²). The findings from this meta-analysis strongly support that the conditions of EBW, overweight, and obesity are all associated with an increased risk of endometrial cancer. Also, the strength of the association increases with increasing BMI.

REFERENCES

Allott EH., Cohen SM., Geradts J., Sun X., Khoury T., Bshara W. (2016). *Performance of Three Biomarker Immunohistochemistry for Intrinsic Breast Cancer Subtyping in the AMBER Consortium*. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2016;25:470-8.

Andreano A., Rechichi G., Rebora P., Sironi S., Valsecchi MG., Galimberti S. (2014). *MR diffusion imaging for preoperative staging of myometrial invasion in patients with endometrial cancer: a systematic review and meta-analysis.* Eur Radiol. 2014 Jun;24(6):1327-38. doi: 10.1007/s00330-014-3139-4. Epub 2014 Mar 26. Review. PubMed PMID: 24668009.

Antonsen SL., Jensen LN., Loft A. (2013). *MRI, PET/CT and ultrasound in the preoperative staging of endometrial cancer – a multicenter prospective comparative study.* Gynecol Oncol 2013;128:300–8.

Bae HS., Lim MC., Lee JS., Lee Y., Nam BH., Seo SS. (2016). *Postoperative lower extremity edema in patients with primary endometrial cancer.* Ann Surg Oncol. 2016;23(1):186-95.

Beesley VL., Rowlands IJ., Hayes SC., Janda M., O'Rourke P., Marquart L. (2015). *Incidence, risk factors and estimates of a woman's risk of developing secondary lower limb 16 lymphedema and lymphedema-specific supportive care needs in women treated for endometrial cancer.* Gynecol Oncol. 2015;136(1):87-93.

Bendifallah S., Canlorbe G., Raimond E. (2015). *External validation of nomograms designed to predict lymphatic dissemination in patients with early-stage endometrioid endometrial cancer: a multicenter study.* Am J Obstet Gynecol 2015; 212: e1–7.

Biglia N., Librino A., Ottino MC., Panuccio E., Daniele A., Chahin A. (2015). *Lower limb lymphedema and neurological complications after lymphadenectomy for gynecological cancer.* Int J Gynecol Cancer. 2015;25(3):521-5.

Bradford LS., Rauh-Hain JA., Schorge J., Birrer MJ., Dizon DS. (2015). *Advances in the management of recurrent endometrial cancer. Am J Clin Oncol 2015; 38: 206–12*.

Burke WM., Orr J., Leitao M., Salom E., Gehrig P., Olawaiye AB., Brewer M., Boruta D., Villella J., Herzog T., Abu Shahin F. (2014). *Endometrial cancer: a review and current management strategies: part I.* SGO Clinical Practice Endometrial Cancer Working Group., Society of Gynecologic Oncology Clinical Practice Committee.. Gynecol Oncol. 2014 Aug;134(2):385-92. doi: 10.1016/j.ygyno.2014.05.018. Epub 2014 Jun 4. Review. Erratum in: Gynecol Oncol. 2014 Dec;135(3):625. Villella, Jeanine [corrected to Villella, Jeannine]. PubMed PMID: 24905773.

Busch EL., Crous-Bou M., Prescott J., Chen MM., Downing MJ., Rosner BA., Mutter GL., De Vivo I. (2017). *Endometrial Cancer Risk Factors, Hormone Receptors, and Mortality Prediction.* Cancer Epidemiol Biomarkers Prev. 2017 May;26(5):727-735. doi: 10.1158/1055-9965.EPI-16-0821. Epub 2017 Jan 4. PubMed PMID: 28052940; PubMed Central PMCID: PMC5413416.

Cheang MC., Martin M., Nielsen TO., Prat A., Voduc D., Rodriguez-Lescure A. (2015). *Defining breast cancer intrinsic subtypes by quantitative receptor expression.* The oncologist. 20:474-82.

Coleman RL., Sill MW., Thaker PH. (2015). *A phase II evaluation of selumetinib (AZD6244, ARRY-142886), a selective MEK-1/2 inhibitor in the treatment of recurrent or persistent endometrial cancer:* an NRG Oncology/Gynecologic Oncology Group study. Gynecol Oncol 2015; 138: 30–35.

Creutzberg CL., Van Stiphout RG., Nout RA. (2015). *Nomograms for prediction of outcome with or without adjuvant radiation therapy for patients with endometrial cancer: a pooled analysis of PORTEC-1 and PORTEC-2 trials.* Int J Radiat Oncol Biol Phys 2015; 91: 530–39.

Deura I., Shimada M., Hirashita K., Sugimura M. (2015). *Incidence and risk factors for lower limb lymphedema after gynecologic cancer surgery with initiation of periodic complex decongestive physiotherapy*. Int J Clin Oncol. 2015;20(3):556-60.

Epstein E., Blomqvist L. (2014). *Imaging in endometrial cancer.* Best Pract Res Clin Obstet Gynaecol. 2014 Jul;28(5):721-39. doi: 10.1016/j.bpobgyn.2014.04.007. Epub 2014 Apr 30. Review. PubMed PMID: 24852891.

Ferlay J., Soerjomataram I., Dikshit R. (2015). *Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.* Int J Cancer 2015; 136: E359–86

Ferlay J., Steliarova-Foucher E., Lortet-Tieulent J. (2013). *Cancer incidence andmortality patterns in Europe: estimates for 40 countries in 2012*. Eur J Cancer 49:1374–1403.

Ferrandina G., Petrillo M., Mantegna G., Fuoco G., Terzano S., Venditti L. (2014). *Evaluation of quality of life and emotional distress in endometrial cancer patients: a 2-year prospective, longitudinal study*. Gynecologic oncology. 2014;133(3):518-25.

Geppert B., Persson J. (2015). *Robotic infrarenal paraaortic and pelvic nodal staging for endometrial cancer: feasibility and lymphatic complications.* Acta Obstet Gynecol Scand. 2015;94(10):1074-81.

Guinney J., Dienstmann R., Wang X., de Reynies A., Schlicker A., Soneson C. (2015). *The consensus molecular subtypes of colorectal cancer.* Nature medicine. 2015;21:1350-6.

Hareyama H., Hada K., Goto K., Watanabe S., Hakoyama M., Oku K. (2015). *Prevalence, classification, and risk factors for postoperative lower extremity lymphedema in women with gynecologic malignancies: a retrospective study.* Int J Gynecol Cancer. 2015;25(4):751-7.

Herling SF., Havemann MC., Palle C., Moller AM., Thomsen T. (2015). *Robotic-assisted laparoscopic hysterectomy seems safe in women with early-stage endometrial cancer*. Dan Med J. 2015;62(8):A5109.

Hopp EE., Osborne JL., Schneider DK., Bojar CJ., Uyar DS. (2015). *A prospective pilot study on the incidence of post-operative lymphedema in women with endometrial cancer*. Gynecol Oncol Rep. 2015;15:25-8.

Howitt BE., Shukla SA., Sholl LM. (2015). *Association of polymerase e-mutated and microsatellite-instable endometrial cancers with neoantigen load, number of tumor-infi ltrating lymphocytes, and expression of PD-1 and PD-L1*. JAMA Oncol. 2015 Dec;1(9):1319-23. doi: 10.1001/jamaoncol.2015.2151.

Hunter Community Study, and the Studies of Epidemiology and Risk Factors in Cancer Heredity. (2015). *Rare germline copy number deletions of likely functional importance are implicated in endometrial cancer predisposition.* Hum Genet 2015; 134: 269–78.

Hussein YR., Weigelt B., Levine DA. (2015). *Clinicopathological analysis of endometrial carcinomas harboring somatic POLE exonuclease domain mutations.* Mod Pathol 2015; 28: 505–14.

Jagsi R., Jiang J., Momoh AO. (2014). *Trends and variation in use of breast reconstruction in patients with breast cancer undergoing mastectomy in the United States.* J Clin Oncol. 2014;32:919-926.

James JA., Rakowski JA., Jeppson CN., Stavitzski NM., Ahmad S., Holloway RW. (2015). *Robotic transperitoneal infra-renal aortic lymphadenectomy in early-stage endometrial cancer*. Gynecol Oncol. 2015;136(2):285-92.

Jayaraman M., Radhakrishnan R., Mathews CA., Yan M, Husain S., Moxley KM., Song YS., Dhanasekaran DN. (2017). *Identification of novel diagnostic and prognostic miRNA signatures in endometrial cancer.* Genes Cancer. 2017 May;8(5-6):566-576. doi: 10.18632/genesandcancer.144. PubMed PMID: 28740575; PubMed Central PMCID: PMC5511890.

Kisu I., Banno K., Lin LY. (2013). *Preoperative and intraoperative assessment of myometrial invasion in endometrial cancer: comparison of magnetic resonance imaging and frozen section.* Acta Obstet Gynecol Scand 92:525–535.

Sala E., Rockall AG., Freeman SJ., Mitchell DG., Reinhold C. (2013). *The added role of MR imaging in treatment stratification of patients with gynecologic malignancies: what the radiologist needs to know.* Radiology 266:717–740.

Mascilini F., Testa AC., Van Holsbeke C. (2013*). *Evaluating myometrial and cervical invasion in women with endometrial cancer: comparing subjective assessment with objective measurement techniques.* Ultrasound Obstet Gynecol 2013;42: 353–8.

Matulonis U., Vergote I., Backes F. (2015). *Phase II study of the PI3K inhibitor pilaralisib (SAR245408; XL147) in patients with advanced or recurrent endometrial carcinoma.* Gynecol Oncol 2015; 136: 246–53.

Mendivil AA., Rettenmaier MA., Abaid LN., Brown III JV., Micha JP., Lopez KL. (2016). *Lower-extremity lymphedema following management for endometrial and cervical cancer*. Surg Oncol. 2016;25(3): 200-4.

Mitra D., Catalano PJ., Cimbak N., Damato AL., Muto MG., Viswanathan AN. (2016). *The risk of lymphedema after postoperative radiation therapy in endometrial cancer*. J Gynecol Oncol. 2016;27(1):e4.

Mutter GL., Prat J. (2014). *Endometrial Adenocarcinoma. Pathology of the Female Reproductive Tract. 3rd ed.* New York: Elsevier; 2014. p. 370-401.

Oza A., Pignata S., Poveda A. (2015). *Randomized phase II trial of ridaforolimus in advanced endometrial carcinoma.* J Clin Oncol 2015; published online June 15. DOI:10.1200/JCO.2014.58.8871.

Rowlands IJ., Janda M., McKinnon L., Webb PM., Beesley VL. (2015). *Prevalence, predictors, and correlates of supportive care needs among women 3-5 years after a diagnosis of endometrial cancer*. Support Care Cancer. 2015;23(5):1205-14.
Siegel RL., Miller KD., Jemal A. (2015). *Cancer statistics, 2015.* CA Cancer J Clin 2015; 65: 5–29.
Siegel RL., Naishadham D., Jemal A. (2013). *Cancer statistics.* CA Cancer J Clin 766 2013;63(1):11–30.
Slomovitz BM., Jiang Y., Yates MS. (2015). *Phase II study of everolimus and letrozole in patients with recurrent endometrial carcinoma.* J Clin Oncol 2015; published online Jan 26. DOI:10.1200/ JCO.2014.58.3401.org.
Thomsen HS., Morcos SK., Almen T. (2013). *Nephrogenic systemic fibrosis and gadolinium-based contrast media:* updated ESUR Contrast Medium Safety Committee guidelines. Eur Radiol 2013;23:307–18.
Todo Y., Yamazaki H., Takeshita S., Ohba Y., Sudo S., Minobe S. (2015). *Close relationship between removal of circumflex iliac nodes to distal external iliac nodes and postoperative lower-extremity lymphedema in uterine corpus malignant tumors.* Gynecol Oncol. 2015;139(1):160-4.
Trabert B., Wentzensen N., Felix AS., Yang HP., Sherman ME., Brinton LA. (2015). *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.
Valu MV., Toma O. (2017). *A retrospective sequential study of t he risk factors and the incidence of the endometrial cancer.* Analele Stiintifice ale Universitatii" Alexandru Ioan Cuza" din Iasi Sec. II a. Genetica si Biologie Moleculara, 18(1), 31-36.
Zaino RJ., Carinelli SG., Ellenson LH. (2014). *Tumours of the uterine corpus: Epithelial tumours and precursors. WHO Classification of Tumours of the Female Reproductive Organs. 4th ed.* Lyon, France: IARC Press; 2014. p. 125-34.

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