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review

Surgical treatment and fertility perservation in endometrial cancer

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Background. Endometrial cancer (EC) represents a high health burden in Slovenia and worldwide. The incidence is increasing due to lifestyle and behavioural risk factors such as obesity, smoking, oestrogen exposure and aging of the population. In many cases, endometrial cancer is diagnosed at an early stage due to obvious signs and symptoms. The standard treatment is surgery with or without adjuvant therapy, depending on the stage of the disease and the risk of recurrence. However, treatment modalities have changed in the last decades, considerably in the extent of lymphadenectomy.

Conclusions. The gold standard of treatment for is surgery, which may be the only treatment modality in the early stages of low-grade tumours. In recent years, a minimally invasive approach with sentinel node biopsy (SNB) has been proposed. A conservative approach with hormonal treatment is used if fertility preservation is desired. If EC is in advance stage, high-risk histology, or high grade, radiotherapy, chemotherapy, or a combination of both is recommended.

Key words: endometrial cancer; uterus, treatment; minimally invasive surgery; laparoscopy

Introduction

Endometrial cancer (EC) is the most common gynaecological cancer in Slovenia and worldwide. Due to the rapid onset of symptoms and good diagnostic possibilities, the majority of cases are diagnosed at an early stage of the disease, which provides good treatment prospects and high overall survival rate.[1]

EC is the fifth most common cancer among women in Slovenia. The average number of new cases per year in 2013–2017 was 305 (29.5/100,000 women) and 61 women died (5.9/100,000 women). EC in 90% of cases occurs in women over the age of 50. The median age at diagnosis is 63 years.[2] Approximately 4% of patients diagnosed with EC are under 40 years of age and wish to preserve their fertility.[3]

In most cases, EC is diagnosed at the early stages of the disease (80% in FIGO stage I), with a five-year overall survival rate of over 95%. However, if the disease is locally advanced or distant metastases are present, the five-year overall survival rate is 68% for locally advanced disease and 17% for distant metastases.[4] In early stage of the disease, surgery alone is the gold standard of treatment. In advanced stage of EC, adjuvant therapy is often suggested, but is not standardized. Adjuvant therapy may include chemotherapy, radiotherapy, or a combination of both.[5] In this article we give an overview of the surgical treatment for EC.

Classification

EC, which accounts for about 98% of cancers of the uterine body, can be divided into two groups according to clinical and pathological characteristics.

EC type I generally has a favorable prognosis. Most tumors in this group are endometrioid carcinomas, but mucinous carcinomas are also included in this group. Type I carcinomas are the result of long-term exposure to estrogen without progesterone. They arise from endometrial hyperplasia or endometrial intraepithelial neoplasia (EIN). In most cases they are well differentiated and are usually detected at an early stage of the disease. Most risk factors are related to estrogen exposure. Risk factors include obesity, hormone replacement therapy, polycystic ovary syndrome, early onset of menarche and late menopause. The most important risk factor is obesity, which increases the relative risk by 2.54.[6] Women who are unable to conceive or have never given birth are also at higher risk.[7] The use of combined oral contraceptives reduces the incidence of EC.[8]

EC type II are aggressive tumours with a worse prognosis. This group includes serous, clear cell, neuroendocrine, mixed-cell, undifferentiated and dedifferentiated endometrial carcinomas and carcinosarcoma. Type II carcinomas are not related to the action of oestrogen. They occur in the atrophic endometrium and are by definition highly malignant or high-grade tumors.[7,9]

All tumours must be histologically verified. Endometrioid carcinomas, which account for 75% of EC, are classified by nuclear grade and architectural pattern.[10] If the tumour has less than 5% of the solid growth pattern, the tumour is classified as grade 1. If 6–50% of solid growth patterns are present, the tumour is classified as grade 2 and grade 3 if it accounts for more than 50% of solid growth patterns.

Mucinous adenocarcinomas have a mucinous appearance in more than 50% of the tumour. They usually have a favourable prognosis. Serous carcinomas have a papillary architecture with atypical mitosis and nucleolus. Clear cell adenocarcinomas have the worst prognosis and different histological patterns, from papillary, glandular to tubulocystic and diffuse. Mixed cell carcinomas combine two or more pure types. In undifferentiated carcinomas there is no differentiation.[11]

Genetic predisposition

EC may also occur in association with various hereditary syndromes or inherited genetic disorders. 2–3% of EC occur in women with Lynch / Hereditary Non-Polyposis Colorectal Cancer syndrome.[12] EC is caused by germline mutations in mismatch repair (MMR) genes, namely MLH1, MLH2, MSH6, and PMS2. People with Lynch syndrome have a 10–80% risk of developing colorectal cancer by age 70 and a 15–60% risk of developing endometrial cancer by age 70.[13] Lynch syndrome carriers are diagnosed with EC at an early age (60% between the ages of 44 and 62).[14] Screening colonoscopy every 1 to 2 years for women with Lynch syndrome is part of the recommendations. The importance of screening endometrial biopsy every 1–2 years after the age of 30–35 years still needs to be proven but is recommended by National Comprehensive Cancer Network (NCCN Guidelines Genetic/Familial High Risk Assessment: Colorectal, Version 1.2020, Lynch syndrome).[15] Prophylactic hysterectomy with bilateral salpingo-oophorectomy is recommended in women who have completed childbearing.[4,16] Cowden syndrome is another, much rarer hereditary cause of EC. A germline mutation in the tumour suppressor PTEN gene is present.[17]

Surgical treatment

The diagnosis of EC must be made before surgery. It can be made by pipelle aspiration, by dilatation of the cervix and curettage or by hysteroscopy with biopsy of the endometrium. Today, hysteroscopy is the most commonly used procedure. There is some evidence of an increased risk of intraperitoneal spread of malignant cells into the abdominal cavity. The reason for this could be the use of distension fluid.[18–20]

The standard treatment for EC is surgery, where minimally invasive surgery has become increasingly prevalent in recent years.[21] Randomised trials comparing laparoscopy and laparotomy for surgical staging of EC reported no difference in detection of overall disease at advanced stages, equal or fewer intra- and postoperative complications with laparoscopic approach and shorter hospital stays.[22,23]

The standard approach for the treatment of early stages EC (FIGO stages IA–IIA) is surgical, with removal of the uterus, ovaries, fallopian tubes and with or without sentinel node biopsy (SNB). The approach can be by laparotomy or minimally invasive by laparoscopy or robotic-assisted laparoscopy. Studies have shown that obese patients and patients with comorbidities also benefit from laparoscopic approach.[24,25]

Young premenopausal patients under 40 years of age usually have early stage disease and low-grade tumours.[26] Artificially induced menopause and its

consequences should be avoided. Therefore, ovarian preservation should be considered in selected cases. Retrospective studies and meta-analysis have shown no effect on overall survival if the ovaries are left *in situ* in selected cases at early stages EC. However, synchronous malignant ovarian tumors must be excluded.[27,28]

Lymphadenectomy has its role in staging of EC. However, there is still no consensus on the therapeutic value, indications and extent of the procedure (pelvic, para-aortic to the inferior mesenteric artery or para-aortic to the left renal vein). The sentinel lymph node is the first lymph node in the lymphatic basin into which the lymph of the primary tumour drains. Histologic examination of the sentinel lymph node is representative of all other lymph nodes in the area, and a histologically negative sentinel lymph node signifies the absence of metastases in other non-sentinel lymph nodes. Indocyanine green (ICG) solution is applied to the cervix, which then fluoresces in infrared light so that the lymphatic pathway can be followed until it enters the sentinel lymph nodes.[29] ICG solution is injected superficially into the cervix at 2 or 4 points (at 3, 6, 9 and 12 o'clock), 1-3 mm below the mucosa. Optionally, the solution can be injected deeper, 1–2 cm into the cervical stroma. This allows excellent redistribution of ICG solution around the uterine vessels and lymphatic basin of the parameterium and broad ligament. SNB is performed in the early stage EC, with no suspicious lymph nodes and/or extrauterine spread on imaging.[30]

SNB is an intermediate step between the omission of radical lymphadenectomy and the renunciation of lymphadenectomy. In 2017, FIRES multicentre prospective study showed that the use of the SNB procedure can safely replace lymphadenectomy in the early stage EC.[31]

While SNB can be falsely negative and fails to detect metastases in 3% of cases, the procedure has the potential to expose fewer patients to the morbidity of a complete lymphadenectomy.[31]

The risk rate for regional lymph node seeding in the group of patients with low and intermediate risk EC is approximately 1.4%.[32,33] The risk that would justify a pelvic lymphadenectomy should reach at least 3%, so in most cases routine pelvic lymphadenectomy is not recommended in this group of patients.[4]

Part of the surgical treatment of high- risk EC is also a complete pelvic and para-aortic lymphadenectomy with the upper border to the left renal vein.[4] In two retrospective studies, it was observed that the overall survival of patients with the removal of more than 10–12 pelvic lymph nodes was longer.[34,35] It is important to remember that in 7–8% of cases para-aortic lymph nodes may also be positive even if the pelvic lymph nodes are negative.[36,37] Therefore, removal of both pelvic and para-aortic lymph nodes is recommended in high-risk EC.[4,36]

In non-endometrioid and other high- risk histologic types, omentectomy is also performed as part of the staging procedure. Studies have shown longer progression-free survival and overall survival in patients in whom complete or optimal cytoreduction has been achieved.[38]

Radiotherapy for inoperable endometrial cancer

In 3–9% of patients, surgery is not an option due to medical comorbidities, advanced age, or patient refusal of surgery. Non-surgical treatment, such as radiotherapy, is available as an alternative for this group of patients. It can be used in early or advanced stage EC.[39] Treatment includes brachytherapy alone or in combination with external- beam radiotherapy (EBRT).[4]

Patients with low grade and stage I EC can be treated with brachytherapy alone. Recurrence usually occurs in vaginal vault, which supports the idea of omitting EBRT. EBRT is part of the treatment regimen for patients with indications for lymphadenectomy (tumor grade II and III and high-risk histology). Patients with stage II-IV disease, regardless of grade, should receive a combination of EBRT and brachytherapy. Overall survival rate ranges from 70% to 80% among inoperable population.[39]

Adjuvant treatment

Risk groups for the use of adjuvant therapy

The classification system for patients with EC divides patients into six groups, namely low-, intermediate-, high-intrmediate-, high risk, advanced and metastatic. The system is based on surgical and clinicopathologic prognostic factors and indicates the prognosis, the disease recurrence rate and determines the indications for further adjuvant treatment.[4] Lymph node metastases are the most important prognostic factor causing increased risk of relapse and a higher mortality rate.[40,41]

Low risk EC are considered, endometriod cancers, stage I, grade 1 and 2 with less than 50% myo-

metrial invasion and no limfovascular invasion. The risk of locoregional recurrence is less than 3% in this group, and therefore adjuvant treatment not recommended.[4,42]

Intermediate risk EC are considered endometrioid cancers, stage I, grade 1 and 2, with 50% or more myometrial invasion and no limfovascular invasion. Adjuvant brachytherapy is recommended to decrease the vaginal recurrence rate. No adjuvant therapy is an option in patients younger than 60 years.[4]

High-intermediate risk EC are stage I, grade 3 endometrioid carcinomas with less than 50% myometrial invasion, with positive or negative limfovascular invasion. This group also includes stage I, grade 1 and 2 endometrioid carcinomas with positive limfovascular invasion, regardless of the depth of myometrial invasion.[4] Without adjuvant treatment, the 5-year recurrence rate in this group is up to 25%.[43]

High risk EC are stage I endometrioid carcinomas, grade 3 with 50% or more myometrial invasion, all stage II and III carcinomas with no residual disease after primary cyoreduction, and all other non-endometrioid histologies.[4] In this group, adjuvant radiotherapy of the whole pelvis is standard. In stage IIIC2 (involvement of paraaortic lymph nodes with or without positive pelvic lymph nodes) extended field radiotherapy should be considered. The 5-year overall survival rate is only 20-60% due to the higher recurrence rate and higher rate of distant metastases.[44]

Radiotherapy is most commonly used as adjuvant therapy for intermediate- to high-risk carcinomas.[45] Chemotherapy is used as postoperative treatment for high-risk stage I and II disease, stage III and IV disease or as primary treatment for unresectable advanced, metastatic, or recurrent disease.[5] The combination of carboplatin and paclitaxel is considered first- line chemotherapy. The purpose of chemotherapy is to prevent the occurrence of distant metastases, and the purpose of concomitant chemotherapy and radiation is to reduce the likelihood of local recurrence.[5,12,46]

Preservation of fertility

EC is rather rare in younger patients, usually with a lower stage and grade, and therefore with a favorable prognosis and a higher 5-year survival rate.[47,48] Approximately 4% of patients with EC are under 40 years of age at the time of diagnosis and have a desire to preserve their fertility.[47] They are still at reproductive age and are postponing motherhood. After careful consideration and counselling, selected patients can be treated conservatively with oral progestin, preserving the uterus and ovaries. This treatment is only possible in women with endometrioid type EC, grade 1, in whom the tumour is confined to the endometrium without evidence of myometrial invasion or spread of disease outside the uterus. Selected patients must have a strong desire for fertility preservation and an age of less than 40 years.[47,49] Patients should be clearly informed that this is not a standard treatment approach. Strong and diffuse immunohistochemical expression of progesterone receptors on endometrial specimens is a reliable predictor of remission, but 50% of patients with negative progesterone receptors also achieve remission.[50] The most important predictive factor for outcome is tumour stage. There is no optimal method to determine the stage of the disease before conservative treatment. Clinical staging of EC remains a challenge. The gold standard for staging remains surgery.[51] Histologic type and grade of tumour should be confirmed by fractional abrasion or hysteroscopy. Magnetic resonance imaging of the abdomen should be performed to more accurately determine the depth of invasion into the myometrium and the possible extrauterine extent of the disease. If the evaluation is still inconclusive, exploratory laparoscopy with peritoneal lavage, SNB, and ovarian biopsy should be considered. There is still a 5–30% chance that the tumour is higher grade or more widespread than indicated by the tests.[51,52]

Medroxyprogesterone acetate and megestrol acetate are the most commonly used oral progestin for conservative treatment of EC. Cyclic (14 days every month) or continuous different dosing regimens are used.[4] In the study published by Kallogianidis and Agorastos, the overall response rate to oral progestin was 73% and the relapse rate was 36%.[48] Levonorgestrel-releasing intrauterine device is an alternative to oral progestin for the conservative treatment of EC. The study published by Pal *et al*. showed similar recurrence and relapse rates to oral progestin.[53] Patient response to treatment should be assessed every 3–6 months with cervical dilatation and curettage. If EC recurrence occurs after initial response, hysterectomy should be suggested.[4]

Total hysterectomy with bilateral tubectomy is also recommended after childbearing has been terminated, even if complete response to conservative treatment has been achieved, as risk factors often persist after treatment has ended.[49]

Follow-up

After completion of primary treatment, women undergo long-term follow-up. The aim of routine follow-up is to detect recurrence and spread of the disease before clinical symptoms appear. Early detection of recurrence allows better treatment modalities to be offered with higher survival rates. Most recurrences occur in the first two years after primary treatment. EC metastases are often found in the vaginal vault, suburethral, pelvis, upper abdomen, and lungs. Regular follow-up appointments also allow the gynaecological oncologist to assess the physical and psychological consequences of treatment.[54]

Conclusions

Due to the high incidence of EC, it must be taken into account that primary prevention is important, especially the reduction of oestrogen exposure. Considered use of hormone replacement therapy has halted the growing trend of EC in recent years. The gold standard of EC treatment is surgery, which may be the only treatment modality for early stage, low- grade tumours. In recent years, a minimally invasive approach with SNB has been introduced. In high grade EC, high-risk hystologies or advanced stage EC adjuvant treatment is recommended. Radiotherapy, chemotherapy or a combination of both is applicable.

When EC affects younger women, hereditary syndromes must be considered. A conservative approach with hormonal treatment is used if fertility preservation is desired.

Regular follow-up by an experienced gynaecological oncologist is crucial for early detection of EC recurrence

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