Review article

Endometrial Cancer and the Role of Hysteroscopy, Dilemmas and Perspectives

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Abstract

Hysteroscopy holds a key role in minimally invasive gynecological surgery, particularly in diagnosing endometrial cancer. Its relevance continues to grow, driven by advances in technology and improved training of gynecological endoscopists. While modern hysteroscopy is a product of contemporary medicine, its roots trace back to early pioneers like Bozzini, who first attempted uterine cavity visualization. For generations, gynecologists dreamed of directly observing intrauterine pathology—a vision made possible today through hysteroscopy. This technique is now indispensable in both diagnostics and treatment of benign and malignant uterine conditions. Croatia has played a leading role in this field. Since 2000, the Croatian Society for Gynecological Endoscopy has organized postgraduate courses in Zabok, training nearly a thousand endoscopists from Southeast Europe. These courses, named in honor of Prof. Kurt Semm, representing the region's longest-running and most respected training in minimally invasive gynecological surgery. Notably, the first laparoscopic hysterectomy in Southeast Europe was performed in 1994 at Zabok General Hospital by Prof. Miroslav Kopjar and Dr. Nikša Knezović. Hysteroscopy has since become a routine part of clinical practice, both diagnostically and therapeutically. With its minimal invasiveness and high diagnostic accuracy—enabled by excellent visualization—it allows for targeted sampling and treatment. The future integration of artificial intelligence promises even more precise and personalized approaches. As the healthcare system faces new challenges, hysteroscopy remains a vital tool in improving outcomes in endometrial cancer care through enhanced diagnostics, minimally invasive treatment, and interdisciplinary collaboration.

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Endometrial cancer in a globalized environment

It is undeniable that recent studies support the continuous increase in the number of new cases of endometrial cancer in women. Estimates indicate that around 142,000 women are diagnosed with endometrial cancer each year worldwide, with around 42,000 dying from the disease each year. Based on statistical and epidemiological research, it is evident that endometrial cancer is most often diagnosed after menopause. Its incidence is highest around the seventh decade of life (1). Endometrial cancer rarely occurs in younger patients, with only 4% in the age group under 40 years (2), and it most often occurs in postmenopausal patients (3). Based on recent literature, we now know that endometrial cancer is the fourth most common malignant tumor in the female population worldwide. It was estimated that there were 65,620 new cases of endometrial cancer in the United States, while 12,590 died in the same year (4).4 The underlying cause of the increase in incidence is believed to be the obesity epidemic and the resulting hyperinsulinemia (5-7).

A review of recent literature confirms that endometrial cancer is the most common gynecological malignancy in Europe and North America. Traditional classification of endometrial cancer is based on clinical and endocrine features or on histopathological features. Subtypes defined by different classification systems correlate to some extent, but there is significant heterogeneity in biological, pathological, and molecular features within tumor types from both classification systems. In this Review, we provide an overview of traditional and more recent genomic classifications of endometrial cancer. We discuss how a classification system that includes genomic and histopathological features to define biologically and clinically relevant disease subsets would be useful. Such an integrated classification could facilitate the development of treatments tailored to specific disease subsets and could potentially enable the delivery of precision medicine to patients with endometrial cancer (8).

The lower number of hysterectomies for benign endometrial pathology has also contributed to the current increase in the incidence of endometrial cancer, but the main cause of this is the increasing prevalence of obesity in the population. Obesity poses challenges for diagnosis and treatment, and more research is needed to offer primary prevention to high-risk women and to optimize survival from endometrial cancer. Early onset of bleeding in postmenopausal women ensures that most endometrial cancers can be cured by hysterectomy. On the other hand, patients with advanced disease have a worse prognosis. Minimally invasive surgical strategies and sentinel lymph node biopsy provide an alternative for our patients. The aforementioned is a very good alternative to classic radical surgical treatment. Adjuvant radiotherapy also reduces locoregional recurrences in cases of intermediate and high risk. Advances in our understanding of the molecular biology of endometrial cancer have paved the way for targeted chemotherapy strategies, and clinical trials in the coming years will determine their benefit in the settings of adjuvant, advanced, and recurrent disease (9).

Endometrial cancer is the fourth most common cancer in the United States after breast, lung, and colon cancer. Risk factors are associated with excessive exposure of the endometrium to estrogens, including estrogen therapy, early menarche, and late menopause. Other risk factors include tamoxifen therapy, nulliparity, infertility or anovulation, and polycystic ovary syndrome. Additional risk factors for endometrial cancer include increasing female life expectancy, obesity, hypertension, diabetes mellitus, and hereditary colorectal cancer (10).

Diagnosis and treatment of endometrial cancer - specificities and challenges

What is a relatively favorable fact, however, is precisely the appearance of vaginal bleeding as a symptom of the disease itself. The mentioned also explains the fact why most women with endometrial cancer are diagnosed at an early

stage. The total five-year survival in endometrial cancer for all stages is about 80%. Endometrial tumors of histological grade I have the best prognosis, and they also respond better to hormonal therapy. Grade II and III tumors have a worse prognosis, with a tendency to relapse. What is really crucial is the fact that surgical treatment is the basic procedure in the treatment of endometrial cancer. It enables accurate determination of the stage of the disease and later determination of further adjuvant treatment for patients who need it.1 As the primary treatment for endometrial cancer is surgery, we all face numerous challenges related to younger patients with endometrial cancer who would like to retain their reproductive capacity. Recently, several studies have been published that indicate encouraging results in the treatment of younger patients with endometrial cancer, specifically with the use of high doses of progestin.3 Conservative treatment may be indicated for younger women who wish to preserve their fertility. It is undeniable that lifestyle changes, such as diet and exercise, can modulate the risk of developing endometrial cancer, as well as prevent recurrence and other comorbidities associated with obesity (5).

Based on the latest knowledge, we review the current molecular classification of endometrial cancer, imaging findings in early and advanced disease, and current treatment strategies, with an emphasis on new systemic therapies for advanced EC. The treatment of endometrial cancer has changed significantly in recent years. Molecular characterization of endometrial cancer has shed new light on the biological behavior of this disease, the International Federation of Gynecology and Obstetrics staging system has recently been revised, and imaging alone has been officially included in the treatment of endometrial cancer. Recent genomic analysis of endometrial cancer has led to the approval of new molecularly targeted therapies and immune checkpoint inhibitors. In addition, imaging alone allows the assessment of myometrial invasion, cervical stromal extension, lymph node involvement, and distant metastases, and plays a key role in treatment planning. Modern treatment strategies, which include surgery, radiation, and systemic therapies, are based on accurate staging and risk stratification. These strategies improve the quality of our treatment and provide patients with a better prognosis (6).

The American Cancer Society recommends that all women over the age of 65 be informed about the risks and symptoms of endometrial cancer and that they be advised to contact their doctor in case of symptoms. According to available literature references, there is currently no evidence to support screening for endometrial cancer in asymptomatic women. In the case of heavy bleeding, it is necessary to first exclude pregnancy in women of reproductive age and determine a complete blood count and determine the prothrombin and partial thromboplastin time. Transvaginal ultrasound is also recommended, as is an endometrial biopsy, which determines the further diagnostic and therapeutic procedure in the patient. The prevailing opinion is that the primary therapy for endometrial cancer is surgical with total hysterectomy and bilateral salpingo-oophorectomy and indicated pelvic lymphadenectomy. Recently, more and more emphasis has been placed on minimally invasive surgical treatment with Sentinel node removal. Pre-invasive endometrial changes can be treated conservatively without atypia, while the presence of atypia requires surgical treatment in endometrial hyperplasia. Postoperatively, in advanced stages, radiation and chemotherapy have their place. Survival in patients with endometrial cancer is determined by the stage of the disease itself. Control of risk factors, such as obesity, diabetes and hypertension, also contributes to the prevention of endometrial cancer (10,11).

Endometrial cancer is staged according to the FIGO classification - International Federation of Gynecology and Obstetrics. Early and accurate diagnostic assessment of disease status is important for optimal treatment planning and prediction of outcome. Preoperative evaluation and workup can help assess local extent and detect distant metastatic disease, guiding the optimal course of treatment. Several imaging

modalities, such as transvaginal ultrasound, computed tomography, and magnetic resonance imaging, are used as tools for preoperative staging of endometrial cancer. Positron emission tomography/computed tomography and, more recently, positron emission tomography/magnetic resonance imaging are also used in the management of endometrial cancer. Cross-sectional imaging, particularly MRI, can detect extensive myometrial invasion or extension of tumor into the cervical stroma, which may alter treatment. Imaging studies can also assess the presence of lymph node involvement and detect local and distant metastatic disease at diagnosis. In addition, imaging methods play a major role in monitoring treatment and patient surveillance, and enable the detection of early disease recurrences (12-15).

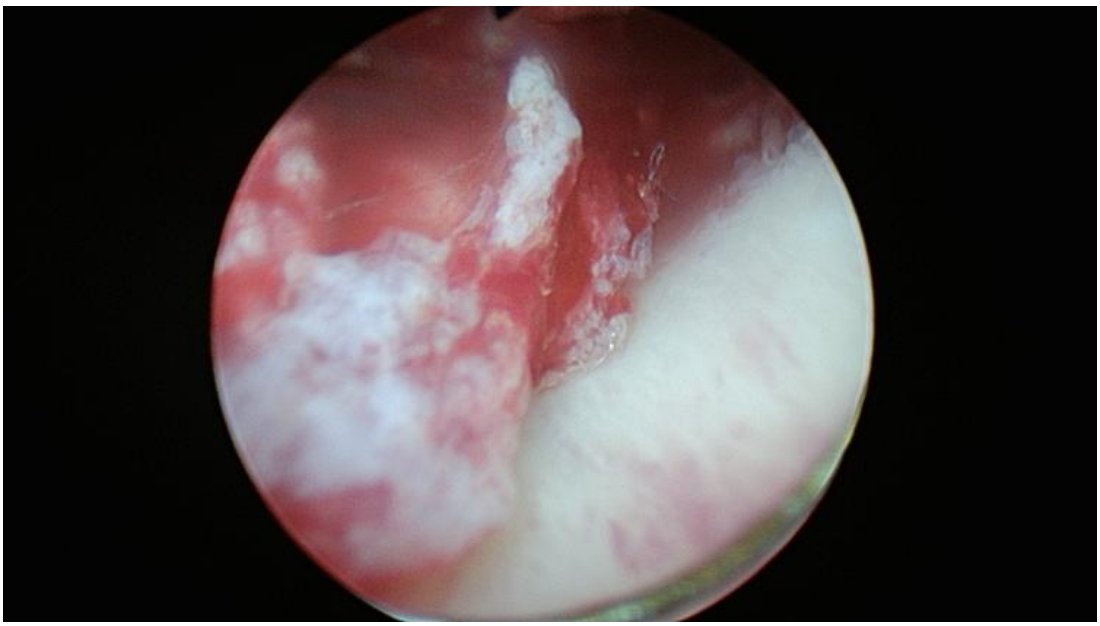

Figure 1. Histoscopic view of endometrial carcinoma

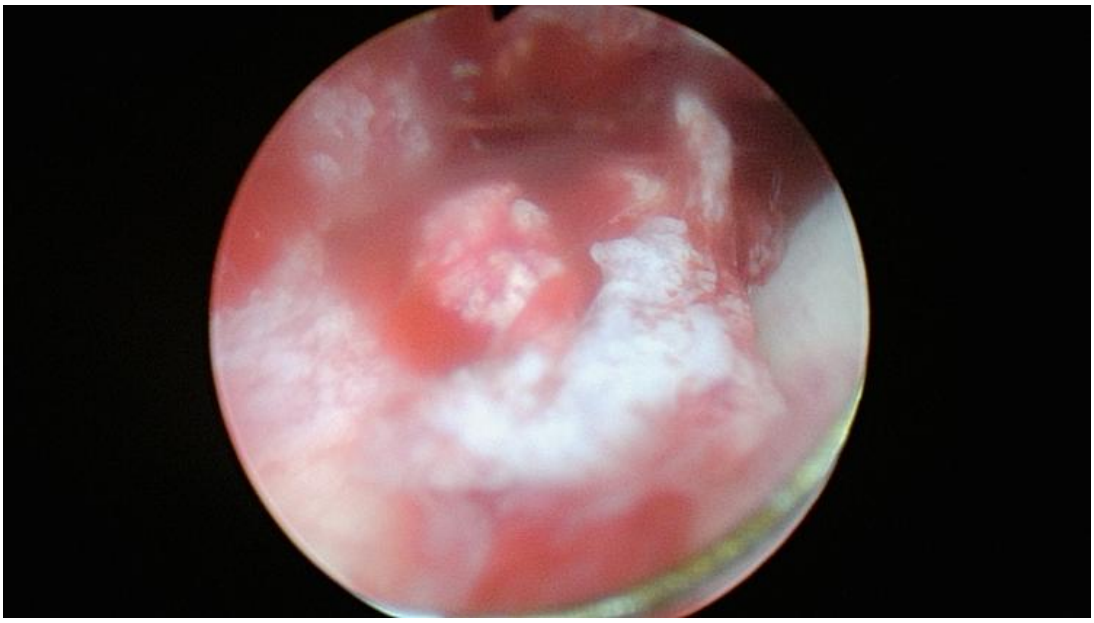

Figure 2. Histoscopic view of endometrial carcinoma

Hysteroscopy in the modern approach to the work-up and treatment of endometrial cancer

With the increase in life expectancy, women now live up to one third of their lives in menopause. Postmenopausal bleeding is a common gynecological complaint encountered by clinicians. Endometrial cancer is present in about 10% of patients with postmenstrual bleeding. However, many other conditions such as endometrial or cervical polyps, genital atrophy, or non-gynecological conditions may also be present. Hysteroscopy has replaced blind diagnostic procedures and is now considered the gold standard in the diagnosis and treatment of intrauterine pathology. Gynecologists in clinical practice should be familiar with the use of hysteroscopy in the diagnosis and treatment of menopausal patients with gynecological complaints (Figure 1 and 2.). Recent findings indicate that there is clear evidence for the role of hysteroscopy in the evaluation and treatment of postmenopausal patients with intrauterine pathology (15).

The Cancer Genome Atlas publication was the first to describe the genomic landscape of endometrial cancer and characterize these cancers into four molecular subtypes with different prognoses. A proactive molecular classifier for endometrial cancer was developed to more easily and inexpensively classify endometrial cancer into four similar molecular subtypes called POLE, mismatch repair deficiency, abnormal p53, and no specific molecular profile. In addition to these four subtypes, other molecular biomarkers may influence clinical behavior and response to targeted therapies and include beta-catenin, Her2 amplification, PI3K/mTOR/AKT alterations, L1CAM, hormone receptor expression, tumor mutational burden, and ARID1A. There are numerous clinical trials investigating treatment escalation and de-escalation within the four molecular subtypes, as well as matching targeted therapies to specific mutational or biomarker profiles. All endometrial cancers should undergo basic molecular classification that includes assessment of mismatch repair status. POLE and p53 status are prognostic and may become useful in the future. Clinicians treating patients with endometrial cancer should understand the role of molecular classification in guiding treatment. This research aims to provide patients with endometrial cancer with the best possible prognosis (7).

Teamwork, involving doctors from many different profiles, at the oncology consultation, determines the treatment, prognosis, and treatment perspectives of our patients, in order to provide them with the best prospects (1). In order to best direct all necessary efforts towards better treatment, monitoring and prognosis of patients with endometrial cancer, it is necessary to respect and accept a number of prerequisites. This includes a detailed review of the etiology, diagnostics, protocols, treatments, monitoring and controversies related to endometrial cancer. It is also necessary to continuously monitor recent literature and guidelines prescribed by relevant societies and institutions. As one of the most common gynecological oncological diseases, endometrial cancer poses great challenges to all of us. In addition to the public health component, endometrial cancer also has a number of other dilemmas for the health system, starting from primary surgical treatment with the very staging of the disease, to adjuvant treatment with irradiation and chemotherapy. In all of the above, patient education will have a major impact on prognosis, as it will help patients cope better with the disease itself, treatment, and subsequent recovery, rehabilitation, and socialization (2). As the prognosis is worse for advanced stages of endometrial cancer, new treatment protocols are being investigated. The goal is to provide an overview of the current state, especially regarding the genetic and metabolic characteristics of the tumor. At the same time, newer technologies are being investigated and nanotechnology tests are being conducted in the early diagnosis of endometrial cancer, the determination of metastases, and the treatment itself. The above is supported by a systematic analysis of recent references taken from Pubmed. Based on the above, it was verified that Hypoxia-inducible Factor-1 and Von Hippel-

Lindau factor participated in the oncogenesis and progression of endometrial cancer, as well as the Nrf2 factor. In addition, various genetic changes were found in endometrial cancer, and it was verified that abnormal inactivation of the X chromosome can also help in the diagnosis of endometrial cancer and its precancerous lesions. Likewise, disorders in glucose and lipid metabolism have been identified in endometrial cancer. Today, therapeutic strategies are focused on the HIF-1α pathway, the mTOR pathway, and immunotherapy. It is evident that endometrial cancer is now understood in many segments, but the underlying mechanisms still remain relatively unknown. This presents challenges for new diagnostic, prognostic, and therapeutic targets, as well as further research (4).

The first joint consensus conference of the European Society for Medical Oncology (ESMO), the European Society for Radiotherapy and Oncology (ESTRO) and the European Society for Gynaecological Oncology (ESGO) on endometrial cancer was held on 11 and 13 December 2014 in Milan, Italy. Four issues were elaborated: prevention and screening, surgery, adjuvant treatment and advanced and recurrent disease. All relevant scientific literature, identified by the experts, was previously reviewed. During the consensus conference, the panel developed recommendations for each specific issue and a consensus was reached. The results of this consensus conference provided evidence-based recommendations for the treatment of endometrial cancer, which greatly helped all professionals who provide multidisciplinary care to patients with endometrial cancer (11).

The prognosis for women with endometrial cancer is generally good. This is because the disease is often diagnosed at an early, treatable stage, as women seek care for postmenopausal bleeding. The prognosis, however, is worse for women with high-risk endometrial cancer. These women may benefit from more extensive surgery, including pelvic and para-aortic lymph node dissection, whereas such surgery is not beneficial for women with low-risk cancer. Therefore, it is important to correctly identify women with high-risk cancer before surgery. Imaging techniques can help us identify and recognize women with high-risk cancer and can help us assess the local extent of the tumor in women with endometrial cancer (13).

Although hysteroscopy is currently the undisputed gold standard for examining the uterine cavity in women with suspected endometrial cancer, it remains controversial as a procedure that may promote the spread of metastases. Endometrial cancer cells can be detached during hysteroscopy and passively transported with the flow of fluid into the peritoneal cavity. There is currently an open debate about the risk of metastases in women undergoing diagnostic hysteroscopy and what conditions must be met for the procedure to be safe. We searched the PubMed, Medline and Scopus databases for data published between 1985 and 2017. The following search criteria were included, "MeSH headings": hysteroscopy, endometrial cancer, intraperitoneal or metastatic spread were used to find relevant papers. Based on the analysis of the data to date, it was concluded that diagnostic hysteroscopy performed in women with endometrial cancer, especially in the early stages, is a very useful, effective and safe diagnostic method. It was also concluded that distension media used for endoscopic procedures in the uterine cavity must be applied at relatively low pressures to prevent an increased risk of intraperitoneal spread of endometrial cancer. This approach reduces the possibility of metastasis (14-16).

Hysteroscopy is performed for many indications. Today, it is common practice for physicians to be trained on hysteroscopic models before performing hysteroscopy on patients. This is due to numerous ethical, legal, and economic constraints associated with the incompatibility of hysteroscopic training on patients. Virtual reality simulation can also be used as a tool for hysteroscopy training. Specific curricula for the training of specific hysteroscopists are also planned. The aforementioned curricula should primarily be based on the requirements for hysteroscopy skills, and their standardization will enable better preparation of future hysteroscopists (16).

Hysteroscopy is today the gold standard in the diagnosis and treatment of intrauterine pathologies because it is a safe and minimally invasive procedure that allows visualization of the entire uterine cavity. In recent years, numerous technological innovations have emerged that have contributed to the development and widespread use of this technique. In particular, new small-diameter hysteroscopes are equipped with an operating channel into which various mechanical instruments can be inserted, and allow not only the examination of the cervical canal and uterine cavity, but also the performance of biopsies or the treatment of benign diseases in a relatively short time. The aforementioned also does not require anesthesia to perform surgical procedures in outpatient settings. In this scenario, the operator must be able to perform hysteroscopy in the correct way to make this procedure as safe and painless as possible for the patient, which requires prior education and experience (16-19).

Regardless of the technological progress we are witnessing, there are still moments in the diagnosis and treatment of endometrial cancer that require thoughtful and team-based multidisciplinary action by experts from many fields. The personalization of medicine and the personalization of the relationship with each individual patient pose numerous challenges to the entire healthcare system. Improving the quality of diagnostics in the treatment of endometrial cancer is an imperative for all of us in our daily clinical work. By improving the quality of our work and continuously improving it, we ultimately contribute to better results in the diagnostics, treatment and monitoring of our patients. The aforementioned approach imposes a paradigm shift in the diagnostic and therapeutic procedure on all of us. It is certain that until recently, in many environments, the diagnostic method of choice was the application of classical fractionated curettage. Fractionated curettage has been routinely used in the detection of endometrial cancer for many years. With the advancement of technology and the experience gained so far, the application of hysteroscopy has provided us with a very high-quality tool in the diagnosis and treatment of endometrial cancer. The great advantages of hysteroscopy are, first and foremost, its minimal invasiveness and very high accuracy, as excellent visualization enables accurate sampling of suspicious samples. All of the above guarantees very good and high-quality results in the diagnosis and treatment of patients with endometrial cancer (20-28).

Conclusion

Endometrial cancer poses new challenges to the public health system, which are increasing, given the continuous increase in incidence and mortality. Minimally invasive treatment, including the use of hysteroscopy in diagnostics, will certainly gain in importance. The major challenges we face every day in the diagnosis, treatment, monitoring and prognosis of patients with endometrial cancer represent a great challenge in our clinical work and impose the need for even better and higher quality care for our patients. Ultimately, the most important thing is to ensure the best and highest quality treatment and prognosis for our patients (29-38).

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Administrative, technical, or logistic support: RF, ŽS, SMM, DF, ŽF, DH, VK, KS

Analysis and interpretation of the data: RF, ŽS, SMM, DF, ŽF, DH, VK, KS
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Karcinom endometrija i uloga histeroskopije, dileme i perspektive

Sažetak

Histeroskopija ima ključnu ulogu u minimalno invazivnoj ginekološkoj kirurgiji, osobito u dijagnostici karcinoma endometrija. Njezin značaj neprestano raste zahvaljujući tehnološkom napretku i sve kvalitetnijem obrazovanju ginekoloških endoskopičara. Iako je moderna histeroskopija rezultat suvremene medicine, njezini korijeni sežu do pionira poput Bozzinija, koji je prvi pokušao vizualizirati šupljinu maternice. Generacije ginekologa sanjale su o mogućnosti direktnog uvida u promjene unutar maternice – san koji je danas ostvaren. Histeroskopija je postala nezamjenjiva i u dijagnostici i u liječenju benignih i malignih promjena maternice. Hrvatska ima vodeću ulogu u ovom području. Od 2000. godine, Hrvatsko društvo za ginekološku endoskopiju organizira poslijediplomske tečajeve u Zaboku, kroz koje je educirano gotovo tisuću ginekoloških endoskopičara iz jugoistočne Europe. Ovi tečajevi, koji nose ime prof. Kurta Semma, najdugovječniji su i najugledniji u regiji. Posebno ističemo da je prva laparoskopska histerektomija u jugoistočnoj Europi izvedena 1994. u Općoj bolnici Zabok, pod vodstvom prof. Miroslava Kopjara i dr. Nikše Knezovića. Histeroskopija je danas rutinski dio kliničke prakse – dijagnostički i terapijski. Zahvaljujući minimalnoj invazivnosti i visokoj točnosti, omogućuje ciljano uzorkovanje i liječenje. Buduća integracija umjetne inteligencije dodatno će unaprijediti preciznost i personalizaciju pristupa. S obzirom na sve veće izazove u zdravstvenom sustavu, histeroskopija ostaje snažno oruđe u poboljšanju ishoda liječenja karcinoma endometrija kroz naprednu dijagnostiku, minimalno invazivno liječenje i interdisciplinarnu suradnju.

Ključne riječi: histeroskopija, karcinom endometrija, dijagnostika karcinoma endometrija