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CONTEMPORARY THERAPIES IN THE TREATMENT OF ENDOMETRIAL CANCER

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Abstract: Endometrial cancer is one of the most common gynecological neoplasms, especially in post-menopausal women, with an increase in cases associated with aging and obesity. Traditionally treated with total hysterectomy and bilateral salpingo-oophorectomy, management has evolved with the use of less invasive and more personalized approaches. Advances in molecular classifications (such as TCGA) allow for better risk stratification and therapeutic targeting, including the use of immunotherapies such as pembrolizumab, which is effective in tumors with microsatellite instability or MMR deficiency. Robotic surgeries, sentinel lymph node biopsy and new diagnostic tools with artificial intelligence have also increased accuracy and reduced morbidity. In young women, fertility preservation strategies with progestogens or levonorgestrel IUDs show good results in early cases. The future of endometrial cancer treatment is moving towards a multidisciplinary and personalized approach, aiming for better survival, less toxicity and a higher quality of life for patients.

INTRODUCTION

Endometrial cancer (EC) is one of the most prevalent gynecological neoplasms in developed countries, with an increasing global incidence pattern in recent years. It is estimated that this neoplasm ranks seventh among all cancers affecting women in the world, with a higher concentration of cases in the 65-75 age group. (Oaknin et al., 2022) In Europe, for example, EC is the most common gynecological cancer, with a five-year prevalence of 34.7% and incidence rates that exceed 120,000 new cases per year. (Concin et al., 2021), 2021) This increase is directly associated with an ageing population and rising obesity rates, a recognized modifiable risk factor for the disease. (Sobel; Simpson; Ferguson, 2021)

The diagnosis of EC is mainly made under clinical suspicion, usually resulting from symptoms such as irregular vaginal bleeding or postmenopause, reported in more than 90% of patients and most cases being diagnosed at an early stage (ANCA-STANCIU et al., 2025). Historically, diagnosis has been based on the invasive collection of endometrial tissue samples; however, recent advances are opening doors to less invasive methods. New diagnostic methods involve protein and DNA biomarkers, as well as cytology, which have great potential to revolutionize diagnostic pathways and enable surveillance in high-risk populations (BAKER-RAND et al., 2024). In addition, the updated classification at molecular development of EC evolution, based on data from The Cancer Genome Atlas (TCGA) and other initiatives, offers a deeper understanding of the disease by dividing it into distinct subtypes: POLE ultramutated, microsatellite instability--high, low copy number and high copy number (ANCA-STANCIU et al., 2025). These molecular insights, increasingly integrated into the updated FIGO staging system, provide a prognostic library with crucial information and guide personalized treatment strategies, symbolizing a shift towards a more personalized paradigm of diagnosis and therapy (BEREK et al., 2023; ANCA-STANCIU et al., 2025).

Due to the generally evident symptomatology in the early stages, endometrial cancer is commonly diagnosed while still in stage I. Traditionally, standard treatment involves total hysterectomy, bilateral salpingo-oophorectomy and pelvic lymph node dissection, with subsequent administration of individualized adjuvant therapy according to definitive histopathological findings (Morice et al, 2016).

Endometrial carcinoma is traditionally classified into two histopathological subtypes: type I, associated with estrogen exposure, with a more indolent behavior and better prognosis, and type II, more aggressive, often diagnosed in advanced stages and responsible for around 70% of deaths from endometrial cancer. (Sobel; Simpson; Ferguson, 2021) More recently, this classification has been complemented by defined molecular profiles, based on *The Cancer Genome Atlas* (TCGA) guidelines, allowing for a more refined prognostic stratification and the individualization of therapeutic approaches (Dellino et al., 2023), 2023). More recent studies have also explored the application of artificial intelligence (AI) in the screening and diagnosis of endometrial cancer, demonstrating an overall sensitivity of 86% (95% CI 79%-90%) and specificity of 92% (95% CI 87%-95%). Magnetic resonance imaging (MRI) with radiomics has emerged as a promising tool for preoperative assessment and risk stratification, providing detailed information on tumor heterogeneity to guide therapeutic decisions (Donato et al., 2023; Wang et al., 2025).

Although the majority of cases are sporadic, 5% to 10% of ECs are related to hereditary syndromes, such as Lynch syndrome, characterized by microsatellite instability and early diagnosis in young women. (Oaknin et al., 2022) In this population, it becomes even more relevant to discuss fertility preservation strategies, especially in the face of stage I diagnosis and active gestational desire. The possibility of conservative therapies has been explored with the use of oral progestogens, levonorgestrel-releasing intrauterine devices and hysteroscopic resection, with increasing rates of complete response in selected patients (Uccella et al., 2022).

According to the meta-analysis by Suzuki et al., 2024, fertility preserving treatment for stage IA EC showed that the proportion of complete response at 12 months was 66% for oral progestins and 86% for levonorgestrel-releasing intrauterine device (IUD). The pooled pregnancy rates were 58% and 44%, respectively.

The typical clinical presentation of EC, such as abnormal uterine or postmenopausal bleeding, contributes to early diagnosis in up to 80% of cases still confined to the uterus. (Oaknin et al., 2022; Sobel; Simpson; Ferguson, 2021) Endometrial biopsy remains the test of choice for diagnostic confirmation, with high sensitivity and specificity, and can be complemented by transvaginal ultrasound when trying to differentiate other causes of bleeding. (Sobel; Simpson; Ferguson, 2021) The standard therapeutic approach involves total hysterectomy with bilateral salpingo-oophorectomy, usually by minimally invasive means, and is even indicated in patients with atypical endometrial hyperplasia, which is considered a precursor lesion to carcinoma. (Uccella et al., 2022), 2022)

However, in recent years, contemporary therapies have emerged that aim not only to control the disease, but also to preserve patients' quality of life and reproductive goals, especially in those diagnosed early. Such approaches include the use of hormonal strategies, molecular classifications for individualized risk stratification, and less invasive surgical therapies, broadening the spectrum of therapeutic possibilities available (Concin et al., 2021; Dellino et al., 2023).

The management of endometrial cancer has become considerably more complex in the last decade, due to various factors. These include changes in histological classifications, which have a direct impact on surgical procedures, the choice of adjuvant therapies and prognostic estimates; changes in the indications for and techniques of lymphadenectomy; the trend towards a reduction in the use of adjuvant therapy, based on evidence from randomized clinical trials; as well as inconsistencies between the different risk stratification systems used to predict recurrence of the disease (Morice et al, 2016).

Given this panorama, it is essential to critically review the current evidence on therapeutic strategies in the management of endometrial cancer, considering technological advances, tumor molecular profile, prognosis and patients' reproductive expectations.

METHODOLOGY

This study is a bibliographic review with the aim of compiling and discussing the most current evidence related to the therapies used in the treatment of endometrial cancer, also taking into account the diagnostic advances presented in recent scientific literature. To select the material, a structured search was carried out in the PubMed database, covering publications from the last five years. The descriptors "Endometrial cancer", "Treatment" and "Diagnosis" were used in combination in order to guarantee the comprehensiveness and accuracy of the results obtained.

Articles that directly or indirectly addressed diagnostic and therapeutic aspects of endometrial cancer were included, as long as they were available in full on the database consulted. Publications in different languages were accepted, as long as they were accessible, methodologically consistent, scientifically relevant and adherent to the theme. Original studies, narrative reviews and update articles were considered eligible. Duplicate publications, studies outside the scope of the research and articles unavailable on the PubMed database were excluded.

RESULTS AND DISCUSSION

Therapeutic advances in endometrial cancer (EC) demonstrate the progressive transition from an exclusively anatomopathological therapeutic model to an integrative approach that combines clinical and histological factors and, more recently, molecular profiles. Total hysterectomy with bilateral salpingo-oophorectomy remains the mainstay of primary

surgical treatment, especially in the early stages of the disease. Selective lymph node assessment, using sentinel lymph node biopsy, has been shown to be effective in defining the risk of recurrence and the need for adjuvant therapy, reducing morbidities associated with systematic lymphadenectomy (Oaknin et al., 2022; Sobel; Simpson; Ferguson, 2021).

Randomized studies, such as LAP2, have shown that laparoscopy has similar rates of overall survival and tumor recurrence when compared to laparotomy, with a lower rate of postoperative complications. In addition, robotic surgery has been shown to be a viable and safe option, especially in obese patients or those at high surgical risk (Oaknin et al., 2022).

A meta-analysis involving 30 studies and 12,025 patients indicated that robotic surgery (RS) for endometrial cancer resulted in lower estimated blood loss, a lower incidence of intraoperative complications and a shorter hospital stay, with a reduced conversion rate compared to laparoscopic surgery (LPS). Compared to laparotomy (LT), CR also considerably reduced blood loss, blood transfusion volume, length of hospital stay, total complication rates (intraoperative and postoperative), as well as readmission and reoperation rates, despite having a longer operative time. Therefore, CR shows superior results in terms of safety profile and efficacy compared to LPS and LT (Liu et al., 2022).

In the context of adjuvant therapy, the integration between traditional clinicopathological factors - such as histological grade, myometrial invasion and presence of substantial lymphovascular invasion (LVSI) - and TCGA--based molecular classification (POLEmut, p53-abn, dMMR and NSMP) has provided refinement in risk stratification. This approach has resulted in individualized therapeutic regimens, with a reduction in unnecessary exposure to chemotherapy and radiotherapy, as well as the possibility of incorporating target therapies (Dellino et al., 2023; Oaknin et al., 2022). Patients with EC mutated for POLE have unfavorable pathological characteristics, indicating intensive adjuvant treatment, however, in a contradictory way, they have shown exceptional clinical results, which leads to concern about overtreatment. Studies indicate that these favorable results may occur independently of treatment, and that patients with non-pathogenic POLE mutations may have worse outcomes (McAlpine et al., 2021).

In addition, it has been observed that patients with PD-1/PD-L1 protein expression or microsatellite instability (MSI-high) respond better to immunotherapy. The use of pembrolizumab, alone or in combination with lenvatinib, has demonstrated an objective response in patients with advanced or recurrent EC, especially in those with a favorable molecular profile, such as POLE mutation or MMR deficiency (Dellino et al., 2023). Recent evidence, including results from phase III trials such as RUBY (NCT03981796), NRG-GY018 (NCT03914612), AtTEnd (NCT03603184) and DUO-E (NCT04269200), has supported the use of immunotherapy for first-line treatment of advanced and metastatic endometrial cancer. Pooled data from 2,320 patients from these trials show that chemotherapy associated with immunotherapy offers a significant improvement in disease progression-free survival compared to chemotherapy alone (HR 0.70, 95% CI 0.62-0.79) in all patient groups, with the benefits being more evident in cases with mismatch repair deficiency (MMRd) or high microsatellite instability (MSI-H). (Bogani et al., 2024)

In cases of endometrial cancer in young women with reproductive desire, conservative therapies with oral progestogens, such as medroxyprogesterone acetate (MPA) and megestrol acetate (MA), have shown complete response rates ranging from 55% to 82%, with pregnancy rates of over 70% in some cohorts.

(Uccella et al., 2022) Although there is still no consensus on the ideal dose and duration, recent studies suggest better outcomes with higher dosage regimens and extended treatment duration, especially in patients without adverse factors such as obesity or insulin resistance.

The data obtained consolidates a paradigmatic change in the treatment of endometrial cancer, which has moved from a uniform approach to a personalized therapeutic model, influenced by molecular and clinical variables. Surgery remains the mainstay of treatment in the early stages, and the preference for minimally invasive approaches, such as laparoscopy or robotic surgery, represents a significant advance in reducing perioperative morbidities, without compromising oncological outcomes. These benefits are particularly evident in patients with obesity, the prevalence of which has increased and is strongly associated with the incidence of type I EC. (Oaknin et al., 2022; Sobel; Simpson; Ferguson, 2021)

The introduction of molecular classification based on TCGA has made it possible to understand the biological heterogeneity of EC. This stratification has become essential to guide adjuvant therapeutic management, identifying subgroups with a high risk of recurrence and worse prognosis, such as p53-abn tumors, as well as those with an excellent response to immunotherapy, such as dMMR and POLEmut (Dellino et al., 2023; Oaknin et al., 2022) The rational use of chemo- and radiotherapy, directed on the basis of these variables, helps to avoid unnecessary treatment in low--risk patients, while at the same time increasing the therapeutic benefit in high-risk cases.

Immunotherapy, especially immune checkpoint inhibitors such as pembrolizumab, is emerging as a promising approach for patients with advanced or recurrent disease. The approval of pembrolizumab for solid tumors with high microsatellite instability or MMR deficiency, regardless of the primary site, represents a milestone in oncological personalized medicine. (Dellino et al., 2023) Although the data is still preliminary, the combination with tyrosine kinase inhibitors, such as lenvatinib, has shown significant response rates, even in patients refractory to previous treatments.

On the other hand, preserving fertility in young women with early EC represents a clinical challenge that requires strict selection criteria and ongoing follow-up. Hormonal therapy with progestogens, especially MA, has been shown to be effective, with higher remission rates in cases of atypical endometrial hyperplasia (AEH) compared to EC itself. Recent studies have shown that high-dose regimens lasting longer than 12 months can increase the likelihood of a complete response, without compromising pregnancy rates or significantly increasing the risk of recurrence (Uccella et al., 2022).

Factors such as high body mass index, insulin resistance and advanced age have been associated with lower response rates, indicating the need for individualized therapeutic planning. Despite advances, there is still a need for well-defined guidelines on the duration of conservative treatment, as well as clinical trials that directly compare different hormonal regimens. The integration of clinical, pathological and molecular data is essential to reliably define which patients can benefit from conservative approaches without compromising oncological efficacy.

There is still a lack of reliable evidence on the correlation between weight loss and fertility preservation or in reducing the risk of recurrence in patients with endometrial carcinoma. Diabetes mellitus does not seem to affect the outcome of conservative treatment in women with atypical hyperplasia (AH), endometrioid intraepithelial neoplasia (EIN) or early endometrial carcinoma. On the other hand, the use of metformin appears to be associated with an improvement in overall survival in patients with endometrial carcinoma and a reduced risk of cancer recurrence (Concin, Nicole et al. 2021).

In short, the contemporary management of endometrial cancer requires a multidisciplinary approach that combines the fundamentals of oncological surgery, advances in genomics and the individual expectations of patients. The future challenge lies in consolidating personalized therapeutic protocols, based on robust evidence, which guarantee better survival rates, minimize toxicities and, when desired, preserve fertility.

CONCLUSION

Advances in endometrial cancer therapies mark a decisive transition from standardized approaches to highly personalized treatments. The incorporation of the molecular classification of TCGA and the growing arsenal of targeted therapies, including immunotherapy, represent a revolution in risk stratification and therapeutic optimization, allowing treatment to be de-escalated in low-risk patients and intensified in cases of greater aggressiveness or recurrence. Another fundamental pillar of treatment is minimally invasive surgery, particularly robotic surgery, with notable perioperative benefits. At the same time, strategies to preserve fertility in young women are showing promising results, although they still require further refinement and standardization.

As far as the diagnosis of the disease is concerned, its evolution is due in part to radiomics and artificial intelligence, which will further improve early detection and tumor characterization. The integration of new diagnostic tools, particularly those using biomarkers and molecular profiles, together with the FIGO staging system, allows for earlier and more accurate identification of the disease and its subtypes. Meanwhile, treatment strategies have evolved beyond traditional surgery to include immunotherapies, targeted therapies and personalized medical treatment, each tailored to the unique molecular characteristics of each tumor. While these innovations have made it possible to achieve better results for patients and significantly reduce mortality rates, there are still significant challenges. Challenges include, among others, optimizing individual treatment administration for multiple patient populations and ensuring equal access to the most advanced care. The future looks promising, especially with the integration of improved accuracy through the further development of Artificial Intelligence-based diagnostic systems, the development of new therapeutic agents and even more individualized treatment options. All of these factors could ultimately contribute to extending survival, minimizing treatment-related morbidity and improving the overall health of individuals affected by endometrial cancer.

It is therefore concluded that the future of endometrial cancer treatment lies in the continuous aggregation of these pillars - advanced molecular diagnostics, innovative target therapies, surgical refinement and preservation of quality of life - with the aim of improving oncological outcomes and each patient's journey.

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