SURGICAL STRATEGIES FOR HIGH-GRADE ENDOMETRIAL CANCER
Temperature-Related Therapies and Prognosis

by

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The relatively low incidence of high-grade endometrial carcinoma (HGEC) poses a significant challenge as it limits the conduct of extensive prospective studies dedicated to identifying the best treatment approach. In most large-scale clinical investigations, HGEC cases are sparsely represented. As a result, the generalizations drawn from these studies may not accurately pertain to HGEC. Herein, we comprehensively review the surgical treatment strategies for HGEC, with a particular focus on the impact of temperature-based therapies, minimally invasive approaches, and molecular subtypes. Our aim is to provide a solid basis for the individualized diagnosis and management of patients afflicted with this condition.

Keywords: *HGEC, surgical strategies, temperature-based therapies, minimally invasive approaches, molecular subtypes, individualized diagnosis, low-incidence cancer*

Introduction

Based on the histomorphological characteristics, HGEC encompasses high-grade endometrial endometrioid carcinoma (HG-EEC) and non-endometrial endometrioid carcinoma (NEEC) [1]. In recent years, there has been a significant upward trend in the proportion of HGEC cases [2]. However, the survival rate of endometrial carcinoma (EC) has not shown a remarkable improvement. This situation largely stems from the dearth of substantial therapeutic progress for patients who are at a high risk of metastasis and recurrence [3].

The standardized and individualized treatment of HGEC requires increased attention from clinicians. In addition to the proper implementation of postoperative adjuvant therapy, determining how to improve patient prognosis through precise preoperative diagnosis and standardized intraoperative assessment has emerged as one of the current research hotspots. This involves a comprehensive understanding of various factors such as the specific subtypes of HGEC, their biological behaviors, and the potential application of advanced diagnostic techniques and intraoperative evaluation methods. Moreover, the exploration of new treatment modalities that can be tailored to the individual needs of patients is also of great significance in this context.

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Choice of preoperative diagnostic methods

In the context of EC, the distinction between HGEC and low-grade endometrial carcinoma (LGEC) is not only important in terms of understanding the disease's nature but also has significant implications for surgical decision-making. The surgical approach and the extent of resection can vary greatly between these two grades. A precise preoperative diagnosis is, therefore, of utmost importance as it directly influences the determination of the most appropriate surgical scope.

Wang *et al.* [4] conducted a comparative study on the diagnostic efficacy of different methods. Their results clearly indicated that hysteroscopic endometrial biopsy had a superior performance in diagnosing endometrial serous carcinoma (ESC) prior to surgery when compared to the traditional curettage method. The significant difference in the diagnostic rates (88.5% *vs.* 65.0%, $P = 0.019$) highlights the potential value of hysteroscopy in improving the accuracy of preoperative diagnosis. However, this seemingly advantageous technique is not without its concerns. During the process of hysteroscopic surgery, the use of uterine expansion media and the application of pressure within the uterine cavity create a complex environment. This environment poses a potential threat as it may facilitate the migration of cancer cells. These cells could potentially gain access to the pelvic cavity through the fallopian tube, or they might spread via the body's natural vascular and lymphatic systems. This iatrogenic tumor dissemination has been a subject of intense discussion within the medical community, with various studies presenting different viewpoints regarding its impact on patient prognosis [5-7].

Positive ascites cytology has emerged as an important factor in predicting the prognosis of EC patients. Previous research has established it as an independent prognostic risk factor, particularly in cases of NEEC [7, 8]. However, the relationship between preoperative hysteroscopy and positive ascites cytology is not straightforward. Larish *et al.* [9] carried out a large-scale retrospective analysis involving 831 HGEC patients. Their findings were rather unexpected as they did not find any evidence to suggest that preoperative hysteroscopy was associated with an increased likelihood of positive ascites cytology, peritoneal dissemination, or disease progression. Similarly, Chen *et al.* [10] focused their analysis on type II EC patients and also failed to detect any significant differences in disease-specific survival (DFS) rates, progression-free survival (PFS) rates, or recurrence sites between the group that underwent hysteroscopy and the group that received diagnostic curettage.

The HGEC is known for its highly aggressive nature, and this characteristic demands that clinicians carefully consider the potential risks associated with any diagnostic or treatment procedures. Preoperative hysteroscopy, in particular, requires a comprehensive assessment of its potential impact on patient prognosis. In the early stages of the disease, the clinical and imaging manifestations of HGEC and type I EC are remarkably similar. This similarity creates a challenge for clinicians as they cannot rely on these common features to accurately predict HGEC. As a result, it becomes difficult to make an informed decision regarding the choice of biopsy methods.

Based on the current body of evidence, it appears that hysteroscopy does not have a significant impact on the spread of tumor cells within the abdominal cavity or on the overall progression of the disease in EC patients. However, it is important to note that type II EC presents unique challenges. The cancer tissue in type II EC is often fragile, with a tendency to hemorrhage and undergo necrosis. This fragility increases the likelihood of cancer cells detaching from the primary tumor site. In light of these characteristics, during hysteroscopic procedures in patients suspected of having type II EC, it is essential to exercise strict control over the uterine distension pressure and to minimize the operation time as much as possible. This approach aims to reduce the potential risks associated with the procedure while still obtaining the necessary diagnostic information.

Choice of surgical approach

In the contemporary medical landscape, the advent and promotion of minimally invasive surgery (MIS) have revolutionized the surgical management of EC. This innovative approach has gained significant traction and has gradually emerged as the standard surgical modality for EC patients. The NCCN guidelines [11] provide clear directives, stipulating that for patients whose tumors are confined within the uterine boundaries, standard surgical procedures should be carried out using MIS. This preference for MIS extends even to cases where the preoperative pathological diagnosis reveals more aggressive subtypes such as ESC, endometrial clear cell carcinoma (ECCC), dedifferentiated/undifferentiated carcinoma, or carcinosarcoma. These recommendations are based on comprehensive evaluations and evidence from extensive clinical research. Similarly, the ESGO/ESTRO/ESP guidelines [12] introduce a note of caution. When tumors have metastasized to other regions within the uterus, the cervix, or have infiltrated the lymph nodes, MIS is considered relatively contraindicated. This is because the spread of the tumor may complicate the minimally invasive procedure and potentially lead to incomplete resection or dissemination of cancer cells during the operation.

The foundation of these guidelines lies in large-scale randomized controlled trials that have rigorously investigated the safety and efficacy of different surgical approaches. The LAP-2 study [13] and the laparoscopic approach to cancer of the endometrium (LACE) study [14] are prime examples of such research endeavors. These studies have convincingly demonstrated the safety of MIS in the context of early stage EC. The results were quite remarkable, showing that survival outcomes in patients undergoing MIS were on par with those receiving open surgery (OPS). Moreover, MIS offered several advantages, including a reduced incidence of complications and an enhanced quality of life for the patients. However, it is important to note that these two studies had certain limitations. They predominantly included patients with relatively low risk EC, and the representation of HGEC within these cohorts was minuscule.

The medical community's perception of MIS in EC was further challenged with the publication of the laparoscopic approach to cervical cancer (LACC) [15]. This led to a wave of re-evaluation and new research initiatives. In 2012, a significant multicenter retrospective study [16] was conducted, specifically focusing on HGEC. This study compared the outcomes of MIS and OPS in a large sample of 383 HGEC patients, encompassing various subtypes such as 122 HG-EEC (31.8%), 120 ESC (31.3%), 44 ECCC (11.5%), and 97 mixed carcinoma (25.3%). The findings were somewhat reassuring as there was no significant difference in PFS between the two surgical groups. This result contributed to the wider acceptance and application of MIS in different pathological types of early stage EC.

Nevertheless, subsequent investigations painted a more complex picture. It was found that in intermediate risk EC patients, MIS was associated with a higher recurrence rate compared to OPS, although there was no significant impact on overall survival (OS) [17, 18]. Philp *et al.* [19] further corroborated this in their study of intermediate and high risk EC, reporting that the MIS group had a significantly shorter median time to recurrence at any site ($P = 0.022$). However, intriguingly, these recurrence risks did not translate into an increased risk of death. In high risk EC patients, especially those with high-grade histologic types or advanced disease [16, 20, 21], the surgical approach did not seem to have a substantial influence on PFS or OS. A meta-analysis published in 2022, which incorporated *post-hoc* analysis of eight retrospective studies and 1 randomized controlled trial, provided additional evidence that MIS did not increase the risk of recurrence or death in HGEC patients [22]. However, this should be interpreted with caution as the high metastasis and recurrence rates inherent in HGEC patients could potentially mask the true impact of the surgical approach on survival. Additionally, the heterogeneity of post-surgical treatments, including adjuvant chemotherapy, radiotherapy, or combined chemoradiotherapy, among these patients further complicates the analysis of the relationship between the surgical method and survival outcomes. Therefore, it is of utmost importance that the choice of surgical approach for HGEC patients be individualized, taking into account all relevant high-risk factors.

Another crucial aspect that has emerged in recent research is the role of molecular classification in determining the optimal surgical approach. Unfortunately, none of the previous studies mentioned above incorporated molecular classification information. This omission has precluded a comprehensive assessment of how the surgical approach affects EC patients with different molecular profiles. Dai *et al.* [23] made a significant discovery in this regard. Their research revealed that MIS was an independent risk factor for recurrence-free survival (RFS) in microsatellite stable (MSS) EC patients (HR = 2.45, 95%CI 1.06-5.64, P = 0.004), particularly in the case of MSS endometrial endometrioid carcinoma. When patients were classified into the tumor mutational burden high (TMB-H) group based on specific gene mutations such as POLE mutation and microsatellite instability high (MSI-H) in tumor tissue, MIS did not have an adverse effect on their prognosis. Moreover, a TCGA-based study demonstrated that, among patients with TP53-mutant EC, MIS was associated with inferior RFS compared with OPS [24]. Based on the observed survival differences across molecular subtypes under different surgical approaches, a molecular feature–guided surgical decision framework was further proposed to inform the selection between MIS and OPS, fig. 1. The underlying mechanism may be related to the stronger *in vivo* anti-tumor immune responses in EC patients with TMB-H, which could potentially counteract the risk of intraperitoneal tumor dissemination associated with MIS [25]. However, in tumors with more aggressive genetic mutations, such as TP53 or CTNNB1 mutations, the risk of recurrence due to MIS is significantly elevated. Moreover, studies have shown that the concordance between molecular subtypes identified in biopsy specimens and those in hysterectomy specimens is higher than that of histopathological diagnosis [26]. This finding highlights the need to reevaluate the current practice of performing molecular subtype analysis after surgery. Utilizing preoperative biopsy specimens for molecular typing could provide valuable information for determining a more rational surgical scope.

The differences between OPS and MIS are not only limited to the surgical techniques but also have implications for potential tumor spread. The main differentiating factors include the use of uterine manipulators, the method of vaginal transection, and the use of CO_2 pneumoperitoneum. These elements can create an environment conducive to tumor spread during the surgical process, either to the vagina or the pelvic cavity. A case control study [27] established a significant link between tumor spillover during MIS (encompassing events such as uterine perforation and exposure of the tumor to extrauterine locations like the vagina or abdominopelvic cavity) and recurrence. The recurrence rate among patients with intraoperative tumor spillover was alarmingly 5.6 times higher than that of those without such incidents. Furthermore, even with the implementation of postoperative adjuvant therapy, the negative impact on survival due to tumor spillover could not be alleviated.

The use of a uterine lifter has been a subject of extensive research and debate. Earlier studies suggested that it did not increase the positive rate of ascites cytology or the recurrence rate of EC patients [28, 29], nor did it have a significant impact on the DFS or OS of HGEC

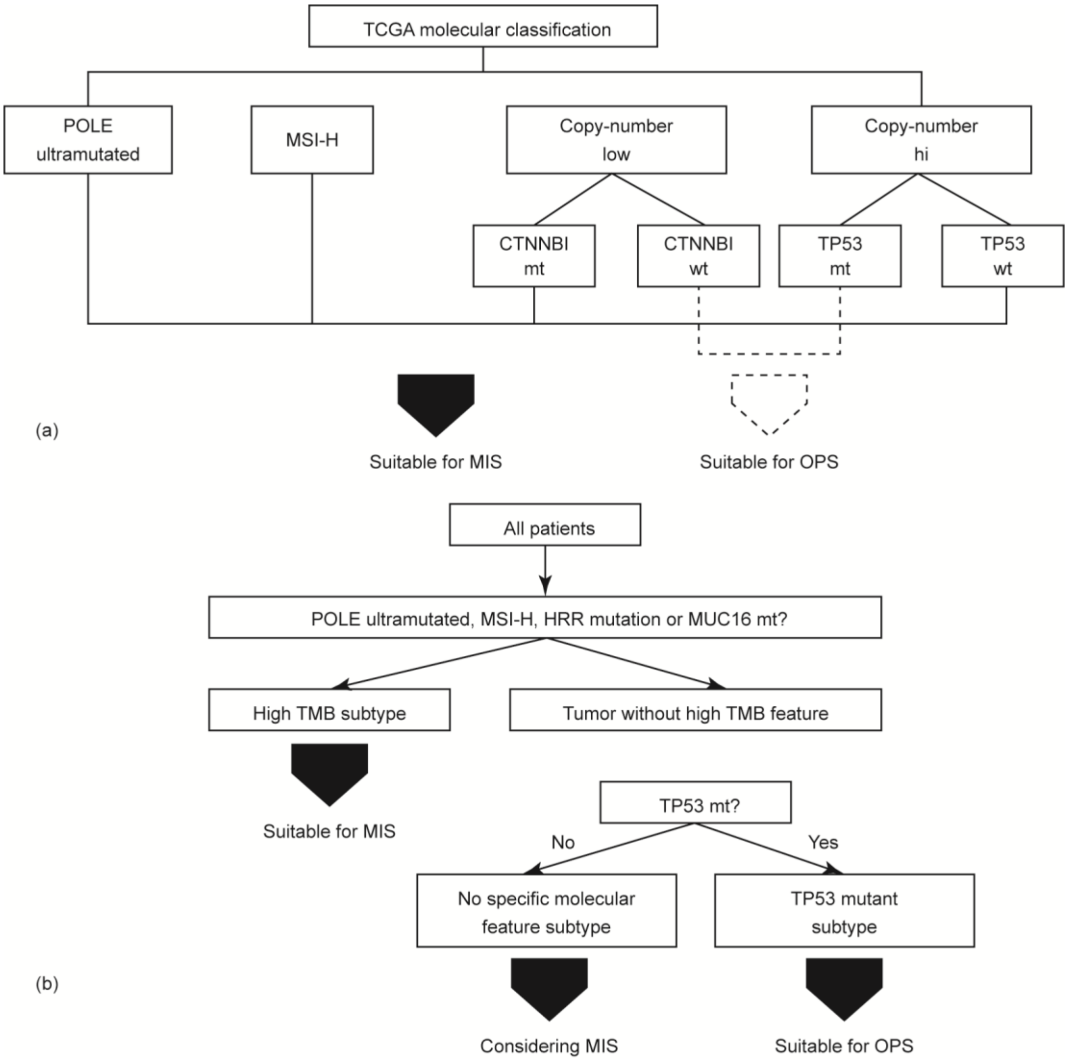

Figure 1. (a) A TCGA-based model for deciding proper surgical approach [24] and (b) a simplified model for deciding proper surgical approach [24]

patients [30]. However, a recent multicenter retrospective study involving 2661 early stage EC patients contradicted these findings. This study reported a higher recurrence rate in patients who used a uterine lifter (11.69% *vs.* 7.4%, $P < 0.001$) and a significantly increased risk of death in patients with EC confined to the uterus ($HR = 1.74$, 95%CI 1.07-2.83, $P = 0.026$) [31]. This new evidence challenges the previously held notion of the safety of the uterine lifter in MIS. In addition, Feigenberg *et al.* [32] investigated whether vaginal removal of a large uterus during MIS increased the risk of recurrence in 758 HGEC patients. Their results indicated that a uterine weight > 75th percentile was associated with an increased risk of abdominal or vaginal recurrence ($OR = 2.207$, 95%CI 1.123-4.337, $P = 0.020$). Currently, the question of whether the use of a uterine lifting device leads to tumor cell dissemination or has a negative impact on prognosis remains highly controversial. In light of this, it is essential to adhere to the principle of tumor-free surgery. Surgical techniques related to uterine lifting and vaginal transection should be continuously optimized to minimize the risk of intraoperative tumor spillover. Additionally, for patients scheduled for MIS, a comprehensive pre-operative physical examination should be performed to accurately assess the size of the uterus and the likelihood of successful complete vaginal removal.

In conclusion, MIS has emerged as the preferred surgical option for early stage EC. In the context of HGEC, although the patient population is relatively small and the malignancy is high, MIS appears to be safe based on current evidence. However, given the aggressive nature of HGEC, more prospective studies are urgently needed to provide conclusive evidence regarding the safety of MIS. Furthermore, the application of molecular classification of EC based on preoperative pathology has not yet been widely adopted, and the potential of this approach to optimize surgical treatment strategies for EC is still in the nascent stages of exploration.

The importance of complete surgical staging

The fundamental surgical procedure for EC consists of total hysterectomy + bilateral adnexectomy ± pelvic lymphadenectomy and para-aortic lymphadenectomy. For HGEC, especially when it comes to type II EC, resection of para-aortic lymph nodes at the level of the inferior mesenteric artery or renal vein is required. In the case of type II EC, comprehensive staging surgery or cytoreductive surgery should be conducted in accordance with the principles of ovarian cancer surgery. Even in the early stages, omentectomy or peritoneal biopsy should be routinely performed [12]. In previous reports, the rate of comprehensive staging surgery among ESC patients ranged from approximately 31.5%-62.3% [4, 33], and for ECCC, it was 44%-52% [34, 35]. A significant number of patients did not meet the requirements stipulated in the guidelines.

Due to the highly aggressive nature of ESC, there is a substantial risk of extrauterine occult metastasis even in the early stages of the disease. Wang *et al.* [36] reported that the metastasis rates of pelvic and para-aortic lymph nodes in ESC patients were as high as 45.2% and 51.5%, respectively. Notably, among 34 patients with para-aortic lymph node metastasis, 2 patients had skipping para-aortic lymph node metastasis without pelvic lymph node metastasis. Hence, systematic resection of retroperitoneal lymph nodes for ESC patients should be emphasized. Chen *et al.* [37] reported that the rate of omental metastasis in ESC patients was 18.7%, and the rate of occult omental metastasis was 9.1%. This not only indicates the high prevalence of omental metastasis in ESC patients but also highlights that macroscopic evaluation and omental biopsy alone may not be sufficient to identify occult metastasis. That is to say, omentectomy should be an integral part of the staging process for ESC patients. Previous studies have emphasized the significance of comprehensive staging surgery for ESC patients: comprehensive staging surgery significantly improves DFS and OS [36] of ESC patients. Even for patients with stage IA ESC whose lesions are confined to the endometrium, staged lymph node resection can significantly enhance patient survival [38]. Therefore, it is crucial to consider the impact of comprehensive surgical staging on ECCC patients as well. In summary, comprehensive staging surgery is of utmost importance for HGEC patients as it enables a better assessment of the patient's stage and guides the selection of postoperative adjuvant therapy. Of course, this is predicated on an accurate preoperative pathological diagnosis.

Different guidelines have slightly varying recommendations regarding omental resection. The NCCN guidelines [11] suggest omental biopsy for patients with ESC, ECCC, and carcinosarcoma, while the ESMO guidelines [39] only recommend omental resection for patients with ESC and carcinosarcoma. The ESGO/ESTRO/ESP guidelines [12] also hold the view that the rate of omental metastasis in clinical stage I ECCC is low [40], and thus omentectomy during the operation may not be necessary. Currently, the mainstream opinion still favors recommending routine omental resection for ECCC patients to avoid overlooking occult omental metastasis. Additionally, there is debate regarding whether omentectomy in non-endometrial endometrioid carcinoma (NEEC) should only be performed when metastatic disease is macroscopically visible or should be carried out routinely under all circumstances. Kaban *et al.* [41] found that micrometastases in the greater omentum accounted for 44.1% of occult metastases in NEEC, and the sensitivity of the surgeon's visual assessment was 0.55. Researchers believe that routine omental sampling is essential regardless of the pathological type of NEEC. However, there is still no definitive conclusion as to whether the resection of normal omentum confers a survival benefit to patients and whether occult metastasis of the greater omentum affects patient survival. Larger-sample-size and prospective randomized controlled trials are required to formulate more targeted clinical guidelines. Molecular classification guides for postoperative adjuvant therapy of early stage EC [42].

Temperature based therapies

Temperature based therapies have emerged as a promising area of research in the treatment of HGEC. These therapies utilize thermal energy to target cancer cells, either alone or in combination with other treatment modalities.

Hyperthermia [43] is one of the commonly studied temperature based techniques. It involves raising the temperature of the tumor tissue to a level that is cytotoxic to cancer cells while minimizing damage to normal surrounding tissues. In the context of HGEC, local or regional hyperthermia can be applied. Local hyperthermia may be achieved through various methods such as interstitial heating probes inserted directly into the tumor tissue. This approach allows for precise temperature elevation within the target area. Regional hyperthermia, on the other hand, can be used to heat a larger area that encompasses the tumor, for example, by using external heating devices that apply heat to the pelvic region. The heat generated during hyperthermia can cause multiple effects on cancer cells. It can disrupt cell membranes, interfere with cellular metabolism, and induce apoptosis. Moreover, hyperthermia has been shown to enhance the effects of chemotherapy and radiotherapy. When combined with chemotherapy drugs, the increased temperature can improve the penetration of the drugs into the tumor cells and increase their cytotoxicity. Similarly, in combination with radiation therapy, hyperthermia can make cancer cells more sensitive to radiation, potentially improving the treatment outcome.

Another temperature based approach is cryotherapy [44]. Cryotherapy involves the use of extremely low temperatures to freeze and destroy cancer cells. In the treatment of HGEC, cryoprobes can be inserted into the tumor under image guidance. The rapid freezing of the tissue causes ice crystal formation within the cells, which leads to cell damage and death. Cryotherapy can be particularly useful for small, localized tumors or as a palliative measure in cases where complete surgical resection is not possible. It has the advantage of being a minimally invasive procedure with relatively low morbidity compared to traditional surgical approaches. However, one of the challenges with cryotherapy is ensuring complete destruction of the tumor cells, as some cells at the periphery of the frozen area may survive and potentially lead to recurrence.

The development of temperature based therapies for HGEC also involves the use of advanced temperature monitoring and control systems. Because the temperature affects greatly the metabolic rates for both human body’s cells and tumor cells [45, 46].

In recent years, micro electro mechanical systems (MEMS) technology [47-49] has shown great potential in this field. The MEMS based devices can be designed to provide real time monitoring within the body during and after treatment. For example, miniaturized sensors can be used to detect changes in tissue conditions, such as temperature, pressure, or biochemical markers related to HGEC. This information can assist surgeons in making more informed decisions during the operation, optimizing the surgical approach based on the actual *in vivo* situation.

Despite the potential benefits, the implementation of temperature based therapies in HGEC treatment also faces several limitations. One of the main challenges is the accurate identification and targeting of the tumor. The complex anatomy of the uterus and the surrounding pelvic structures can make it difficult to precisely apply the thermal treatment only to the cancerous tissue. There is also a lack of large-scale clinical trials to fully evaluate the long term efficacy and safety of these therapies. Moreover, the combination of temperature based therapies with other standard treatments such as surgery, chemotherapy, and radiotherapy requires careful optimization to determine the most effective treatment sequence and dosing regimens. Future research should focus on addressing these limitations to further develop and integrate temperature based therapies into the comprehensive treatment of HGEC.

Conclusions

The HGEC is an extremely aggressive disease, and consequently, its treatment strategy demands high precision and personalization. Given the high degree of malignancy of HGEC and the complexity associated with heterogeneous postoperative treatments, additional prospective studies remain essential to validate the safety of minimally invasive surgery.

In recent years, advances in miniaturized sensing and monitoring technologies have opened new possibilities for real-time intraoperative and postoperative assessment in HGEC, supporting more informed surgical decision-making.

Simultaneously, the potential value of molecular subtyping in guiding surgical procedures has been receiving increasing attention. Specifically, the combination of molecular characteristics to optimize the surgical method and scope holds the promise of improving patient prognosis. This approach could potentially revolutionize the way we approach the surgical management of HGEC, taking into account the unique molecular profiles of each patient to tailor the most effective treatment plan.

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