ORIGINAL RESEARCH ARTICLE

Predictive Factors and Outcomes in the Management of Stage IB Endometrial Cancer: A

Retrospective Study on Recurrence and Adjuvant Treatment Mari Uyeda

Keywords: Endometrial Cancer, Stage IB, POLE, Radiotherapy, Recurrence; Health Management;

ABSTRACT

Background: Endometrial cancer is one of the most common gynaecological malignancies, especially in postmenopausal women. This case study analyzes the clinical course of a 52-year-old female patient diagnosed in April 2020 with low-grade endometrioid adenocarcinoma, stage IB by the FIGO system. After total hysterectomy with bilateral salpingo-oophorectomy, the patient underwent adjuvant radiotherapy due to the presence of risk factors, such as obesity and limited myometrial invasion. Despite the favourable prognosis associated with the ultra mutated POLE molecular profile, the patient presented metastatic recurrence three years after the initial treatment.

Methodology: This was a retrospective analysis of the patient's clinical data, including medical history, therapeutic interventions, and outcomes. Management of recurrence included systemic chemotherapy with carboplatin and paclitaxel, associated with palliative radiotherapy for local control. The investigation detailed the factors that contributed to clinical failure, such as obesity, characteristics of the occupational environment, and limitations of the therapeutic strategies adopted. Results: Partial control of metastatic disease, with reduced symptoms and improved quality of life during treatment of recurrence. However, the disease progressed systemically approximately 18 months after intervention, leading to death in a comprehensive palliative care setting. This case highlights the importance of integrative approaches in managing endometrial cancer, considering the interaction between clinical, molecular and psychosocial factors. Clinical failure in the presence of a favourable molecular profile reinforces the need for more personalized therapeutic strategies, including the use of immunotherapy in specific scenarios. Conclusion: The integration of innovative therapies, improved monitoring protocols, and psychosocial support are critical to optimizing outcomes in patients

protocols, and psychosocial support are critical to optimizing outcomes in patients with gynecologic cancer. This case highlights the relevance of additional studies exploring the combination of technological advances and patient-centred care to address the challenges of this condition.

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What do we already know about this topic?

Stage IB endometrial cancer is characterized by tumour invasion into the myometrium, the muscular layer of the uterus, without affecting nearby structures, such as the cervix. Studies on this type of cancer have shown that there are several predictive factors that influence the risk of recurrence and clinical outcomes. Among these, the histological type of the tumour stands out, with significant differences between types such as endometrioid and serous, as well as the tumour grade, which indicates the level of aggressiveness of cancer. In addition, the analysis of molecular biomarkers, such as POLE mutations, p53 expression and microsatellite instability (MSI), has contributed to a more detailed understanding of the behaviour of the cancer. These factors have helped to personalize treatments and predict prognosis more accurately. When it comes to treatment, low-risk patients are usually treated with hysterectomy alone. However, for those at higher risk, adjuvant treatments such as radiotherapy or chemotherapy are often indicated to reduce the chances of recurrence. In recent years, immunotherapy-based therapies have emerged as a promising alternative, especially in cases associated with high mutational load or immunogenic biomarkers. Recurrence of stage IB endometrial cancer, although not common, can occur in cases with greater aggressiveness or failure of initial treatment. The most frequent sites of recurrence include the pelvic region and nearby lymph nodes. However, early identification of predictive factors and appropriate treatment management have the potential to significantly improve clinical outcomes. This topic remains an area of intense study, with the aim of refining management strategies and improving therapeutic options to benefit patients in a broader and more individualized way.

What is the main contribution to Evidence-Based Practice from this article?

The main contribution of the article "Predictive Factors and Outcomes in the Management of Stage IB Endometrial Cancer: A Case Study of Recurrence and Adjuvant Treatment" to evidence-based practice lies in the detailed identification of predictive factors that influence the recurrence of stage IB endometrial cancer and in the analysis of outcomes associated with adjuvant treatment. Through the presented case study, the article offers a practical and data-driven view on how clinical, pathological and molecular characteristics can guide therapeutic decision-making. In addition, the article seeks to integrate specific findings of the study with the broader context of the medical literature, providing support for more personalized and effective management strategies. This approach has the potential to improve patient care, reducing the risk of recurrence and optimizing clinical outcomes. By focusing on a real case and its implications, the work contributes to the practical application of theoretical concepts in clinical settings, strengthening the evidence base for more informed decisions tailored to individual needs.

What are this research's implications towards health policy?

The study contributes to the theoretical foundation by exploring how molecular biomarkers, such as mutations in POLE, p53, and microsatellite instability, influence clinical outcomes and recurrence risks. These findings expand the understanding of the biological mechanisms underlying stage IB endometrial cancer, offering new insights into tumor behavior. They also reinforce hypotheses about the role of high mutational load in tumors, stimulating research on immunogenicity and personalized treatments. In clinical practice, the article provides direct support for the personalized management of endometrial cancer. By identifying predictive factors and correlating them with treatment outcomes, it guides healthcare professionals in choosing the most appropriate therapeutic approaches, such as the indication of adjuvant treatments (radiotherapy, chemotherapy, or immunotherapy) in specific cases. In addition, it highlights the importance of detailed assessments of molecular biomarkers as part of the diagnostic and therapeutic decision-making protocol, optimizing efficacy and minimizing risks. In terms of policy, the article may influence clinical guidelines and standards of care for patients with endometrial cancer. By highlighting the relevance of molecular testing, it suggests the need for greater access to advanced diagnostic technologies. It may also reinforce the case for including modern therapies, such as immunotherapies, in health care systems and insurance coverage, promoting equity and better outcomes for patients. This type of academic work is an important step towards integrating scientific advances into practice and policy decisions, fostering more evidence-based and patient-centered care.

Authors' Contributions Statement:

Uyeda, Mari sole author of the manuscript through observation and monitoring of a patient.

Introduction

Endometrial cancer is one of the most prevalent gynaecological neoplasms in women, particularly in developed countries (Nair et al., 2023; Zouridis et al., 2023). In Brazil, endometrial carcinoma is estimated to account for 3% of all neoplasms diagnosed in women, ranking behind skin, breast, cervical, colon and stomach tumours (INCA, 2023). 7,840 cases are estimated for the three years 2023 to 2025,

representing an increase of almost 20% compared to the records for 2022, with an estimated risk of 7.08 new cases per 100,000 women (INCA, 2023). More than 90% of cases occur in women over 50 years of age (average age 63 years), contributing to 1% to 2% of all causes of cancer death in the world. The most common symptom is vaginal bleeding and, if diagnosed soon after the onset of symptoms in more than 75% of patients, the disease will be



restricted to the uterus, therefore in an early stage, with a favourable prognosis and high overall survival rates (80% to 85%) in the five years (Datta et al., 2023).

Adjuvant radiotherapy (RT) is often used as a therapeutic strategy in the early stages, especially in cases with intermediate or highrisk factors. In case of treatment failure, the sites of recurrence can be classified as: locoregional recurrence (when involving the pelvis, vaginal vault or vagina) and distant recurrence (intra-abdominal, bone, lung, etc.) (Creutzberg et al., 2000; Keys et al., 1998; Horowitz et al., 2002). There is evidence that when analyzing prognostic factors, there is a reduction in disease-free survival (DFS) at five years.

Methodology

Patient and Clinical Context

A 52-year-old postmenopausal woman was diagnosed with low-grade endometrioid adenocarcinoma in April 2020 at the Oncology Hospital in the city of São Paulo, Brazil, classified as stage IB according to the International Federation of Gynecology and Obstetrics (FIGO) system. The diagnosis was made after presenting symptoms of abnormal vaginal bleeding, prompting a more detailed clinical investigation. Histopathological examination revealed myometrial invasion was limited to 20% of the myometrial thickness. In addition to the diagnosis of endometrial cancer, the patient has a clinical history of obesity, with a body mass index (BMI) of 32, and arterial hypertension controlled by medication (Atenolol 50 mg, once a day), conditions that are recognized as risk factors for the development of endometrial cancer. There is no record of diabetes mellitus or other metabolic conditions, although her history of

obesity suggests potential chronic systemic inflammation. She has no significant history of previous gynaecological diseases, such as fibroids or endometriosis.

Regarding her reproductive history, the patient had two full-term vaginal deliveries and has no history of spontaneous or induced abortions. She did not use hormonal contraceptives for prolonged periods and went through menopause at age 48, with no significant associated complications. Family history reveals that her mother was diagnosed with breast cancer at age 65, which may indicate a moderate genetic predisposition to developing neoplasms. There are no other recorded cases of gynaecological or colorectal cancer among close family members.

From an occupational perspective, the patient worked for 30 years as a teacher in a public school on the outskirts of São Paulo, which implies a work environment with high emotional demands and exposure to chronic occupational stress. This professional activity, combined with the pressures of her routine, may have contributed to high levels of stress, which are known to impact the immune system. Her routine included long working hours, few breaks, and difficulties in maintaining a balanced diet due to her intense schedule.

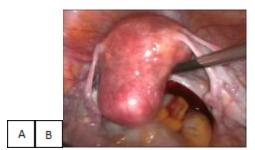
As for her lifestyle, the patient reports being sedentary, which may have contributed to her obesity. Her eating pattern is rich in carbohydrates and ultra-processed foods, with irregular consumption of fruits and vegetables. The patient has never smoked, but occasionally consumes alcoholic beverages in social situations, usually in moderate quantities. She does not practice any regular physical activity, although she acknowledges the medical recommendation to do so. After diagnosis, the patient underwent a total hysterectomy with bilateral salpingo-oophorectomy in May 2020,



a procedure performed without surgical complications, as demonstrated in Figure 1. Pathological analysis confirmed negative margins, with no evidence of lymph node involvement or distant metastases. After initial diagnosis and successful surgical treatment in May 2020, the patient underwent adjuvant RT due to associated risk factors, such as obesity and the presence of limited myometrial invasion (20%). The adopted protocol included a total dose of 45 Gy of pelvic RT, administered in regular fractions over six weeks, to reduce the risk of local recurrence and improve the overall prognosis. During the initial two years

of follow-up, the patient remained in good general condition, with no evident signs of disease recurrence. Follow-up included quarterly consultations, imaging tests (pelvic ultrasound and computed tomography, as necessary), and tumour marker dosage (CA-125). Patient reports indicated mild fatigue and transient gastrointestinal changes related to RT, which were successfully managed with symptomatic measures. Psychologically, she experienced moderate levels of anxiety during follow-up, especially around routine appointments, but demonstrated resilience and significant emotional support from her family.

Figure 1. Total hysterectomy with bilateral salpingo-oophorectomy





In images 1A and 1B we can see a total hysterectomy with bilateral salpingo-oophorectomy, where the patient had her uterus and fallopian tubes removed. The image highlights the absence of these structures in the surgical field, with the surrounding tissues carefully treated to avoid bleeding and ensure the patient's proper recovery.

In early 2023, approximately three years after initial treatment, the patient began to experience symptoms suggestive of disease progression. Symptoms reported included persistent pelvic pain, elevated CA-125 levels in routine laboratory tests, and occasional episodes of abdominal discomfort. Additional examinations, including computed tomography (CT) and magnetic resonance imaging (MRI), confirmed the presence of metastatic lymphadenopathy in the pelvic and retroperitoneal regions, characterizing the clinical failure of the initial therapy. Confirmatory biopsy revealed malignant tissue with histopathological features consistent with the primary tumour.

A retrospective evaluation of factors associated with the risk of recurrence indicated that the combination of obesity, chronic occupational stress, and family history of cancer could have played an important role in disease progression. Although the ultra-mutated DNA polymerase epsilon (POLE) molecular subgroup is generally associated with a favourable prognosis, the interaction between clinical factors and the patient's overall profile probably contributed to the recurrence. Additionally, the patient may have benefited from complementary therapies that were not initially included in the protocol, such as immunotherapies or personalized approaches based on her molecular classification. The



absence of these complementary therapies may have limited the options for controlling the disease at subclinical levels.

After confirmation of clinical failure, a new therapeutic approach was discussed with the patient, including the following options: Systemic chemotherapy (CT): A carboplatin and paclitaxel-based chemotherapy regimen was initiated, focusing on controlling metastatic disease.

Salvage RT: Additionally, a focused dose of RT in the retroperitoneal region was considered for symptomatic relief.

Psychological support: Specialized psychological support was recommended to help the patient deal with the emotional impact of disease recurrence and the challenges of treatment.

There is complexity in the management of early-stage gynaecological cancers, especially in patients with systemic risk factors such as obesity and family history. It is important to use personalized therapeutic strategies that consider both clinical factors and molecular profiles to optimize long-term results. The patient demonstrated great resilience throughout the disease, highlighting the importance of family and psychological support in coping with cancer. This case highlights the need to improve post-treatment follow-up protocols, introducing more advanced monitoring technologies and innovative therapeutic approaches for patients in similar situations.

Treatment of Clinical Failure and Recurrence

After the detection of disease recurrence, confirmed by metastatic lymphadenopathy in the pelvic and retroperitoneal region, the multidisciplinary team decided on a treatment based on the advanced stage of the disease, clinical history and previous treatments. The

strategies adopted included: Systemic therapy with CT given the metastatic involvement and a combined CT regimen was initiated, considered the standard treatment for controlling advanced or recurrent endometrial cancer. The medication used was Carboplatin and Paclitaxel. Carboplatin was selected for its efficacy profile in combination with gynaecological cancers, in addition to being better tolerated compared to cisplatin. Paclitaxel was included due to its robust cytotoxic activity against endometrial tumour cells. Treatment consisted of 6 cycles administered every 3 weeks, with careful monitoring of hematologic adverse effects (such as neutropenia) and other related side effects. Rescue RT was performed as a form of local control and to manage symptoms associated with the metastatic mass, with focused palliative RT. The target was the affected lymph nodes in the pelvic and retroperitoneal regions. The dose was 30 - 40 Gy, administered in daily fractions to control pain and reduce local tumour progression, to provide symptomatic relief and increase the patient's quality of life (QoL) during the disease.

Given the molecular classification of the tumour (ultra-mutated POLE subgroup), the patient was evaluated as a candidate for immunotherapy with immune checkpoint inhibitors, such as Pembrolizumab. Although initially not available in the local protocol, the team explored its inclusion in clinical studies due to the potential for favourable response in tumours with a high mutational load. During treatment, the patient experienced episodes of nausea, alopecia, and fatigue, which were managed with antiemetic medications and nutritional support. There was transient gastrointestinal irritation, which was treated with dietary changes and symptomatic medications. During treatment, the patient



received regular psychological support to deal with the emotional impact of the diagnosis of recurrence and the challenges of the new treatment. The patient responded partially to chemotherapy, presenting a significant reduction in the size of the pelvic metastatic masses, which resulted in decreased pain and overall clinical improvement. Salvage RT was successful in alleviating local symptoms, providing greater comfort and QOL. After 6 cycles of chemotherapy, imaging tests showed partial control of the disease. No progression to new sites was identified during immediate follow-up. However, the previously affected lymph nodes remained present, although smaller, indicating an incomplete response to treatment.

The palliative nature of therapies was discussed with the patient and her family at this stage of the disease. Monitoring with a focus on QOL, including rigorous symptom control, was proposed. Inclusion in a clinical immunotherapy trial was considered, but was not possible due to restrictive eligibility criteria at the time.

In the second half of 2024, approximately 18 months after the recurrence was detected, the patient presented new disease progression, with systemic involvement confirmed on imaging tests. Despite comprehensive palliative care, which included multidisciplinary support and pain management, the patient died peacefully, surrounded by her family, approximately four years after the initial diagnosis of endometrial cancer.

Discussion

The molecular classification of the tumour, especially the ultra-mutated POLE subgroup, is generally associated with a good prognosis due to the high rate of mutations, which tend to induce greater immunogenicity and better

therapeutic response (Slack, Young, Rushton, & British, 2012). Despite this, in this case, there was progression to lymphatic metastasis years after the initial treatment, indicating that additional factors influenced the clinical failure. The interaction between favourable molecular characteristics and clinical risk factors, such as obesity, myometrial invasion, and the absence of specific complementary therapies, may have played a critical role in the recurrence. The patient's obesity, with a BMI of 32, is a well-recognized risk factor for endometrial cancer and its progression. This factor is associated with chronic inflammatory processes, hormonal dysfunctions, and greater insulin resistance, which can favour the tumour microenvironment and reduce the efficacy of treatments. Furthermore, obesity can directly affect drug delivery and hinder radiotherapy planning, contributing to suboptimal outcomes (Elshaikh et al., 2016). The patient's occupational history also points to the impact of chronic stress on her general health and immunity, which are often overlooked aspects that can influence the risk of recurrence and therapeutic response (Hansen et al., 2013). This case highlights the need to consider psychosocial factors in treatment planning and long-term follow-up (Charbotel et al., 2013). The clinical failure highlighted in this case also raises questions about the limitations of the initial therapeutic protocol. Although adjuvant RT was successful in preventing immediate recurrence, the palliative nature of treatment during recurrence emphasizes the need for greater personalization in initial approaches. Early introduction of innovative therapies, such as immunotherapies based on immune checkpoint inhibitors, could have been a valuable option for this patient, given the mutational burden of the POLE subgroup. This study highlights the importance of continuous and more sensitive monitoring,



considering the time elapsed between initial treatment and the onset of recurrence. More advanced imaging techniques and accurate biomarkers can provide earlier signs of progression, allowing for more timely therapeutic interventions.

Despite the limitations in fully controlling metastatic disease, multidisciplinary management during recurrence significantly contributed to the patient's quality of life. Psychological support was essential to help her cope with the emotional challenges of progressive disease and to promote a sense of dignity and peace at the end of her journey.

Conclusion

This case study highlights the complexity of endometrial cancer management, highlighting the interdependent role of clinical, molecular, and systemic factors in prognosis and response to treatment. The patient, diagnosed with low-grade endometrioid adenocarcinoma in stage IB, initially demonstrated a favourable response to standard treatment, which included total hysterectomy and adjuvant RT. However, lymphatic recurrence three years after initial treatment highlights the need for a more personalized and integrative approach to oncological care.

Factors such as obesity, family history of cancer, and occupational stress were determinants of the risk of recurrence.
Furthermore, although the ultra-mutated POLE molecular subgroup is generally associated with a good prognosis, it was not sufficient to

prevent clinical failure in this patient, suggesting that therapeutic management could benefit from additional interventions, such as immunotherapy or intensified biomarker surveillance.

The partial response to treatment of recurrence with carboplatin and paclitaxel-based chemotherapy and palliative RT improved the patient's QoL and partially controlled symptoms but did not prevent metastatic progression. This case reinforces the importance of incorporating innovative therapies and exploring multidisciplinary strategies to optimize outcomes, especially in the context of recurrence. Multidisciplinary management focused on OoL, including psychological support and symptom control, provided the patient with a dignified and compassionate approach in the final stages of the disease. Future advances should prioritize the integration of emerging technologies and patient-centred approaches to maximize therapeutic benefits and minimize the risks of recurrence.

Abbreviations

BMI - Body Mass Index, FIGO - International Federation of Gynecology and Obstetrics,
POLE - DNA polymerase epsilon, CT Chemotherapy, QV - Quality of Life, MRI Nuclear Magnetic Resonance, RT Radiotherapy, SLD - Disease Free Survival, CT Computed Tomography.

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