Thesis

Preoperative selection criteria for cytoreductive surgery in advanced endometrial cancer

submitted by

Amra Pasic

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Assoz. Prof. Priv.-Doz. Dr^{in}. Gerda Trutnovsky

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Declaration of Academic Integrity

I hereby confirm that the present diploma thesis is the result of my own independent scholarly work. I also confirm that in all cases, where material from the work of others (in books, articles, essays, dissertations, and on the internet) is acknowledged, quotations and paraphrases are clearly indicated. No material other than that cited in the reference list has been used. I have read and understood the Medical University's regulations and procedures concerning plagiarism.

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Graz, July 17, 2025 Amra Pasic m.p.

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Zusammenfassung

Hintergrund: Die Fragestellung der Diplomarbeit orientiert sich an der geplanten AGO/ENGOT Studie "Evaluation of preoperative clinical and translational selection criteria for cytoreductive surgery in endometrial cancer". Es soll erforscht werden, welche Patientinnen mit fortgeschrittenem/rezidivierendem Endometriumkarzinom am ehesten von einer radikalen operativen Therapie profitieren.

Methodik: Es handelt sich um eine retrospektive Analyse von Patientinnen mit fortgeschrittenem (FIGO IV) oder rezidivierendem Endometriumkarzinom, die zwischen 2011 und 2020 am LKH Graz diagnostiziert und behandelt wurden. Die Patientinnen wurden in eine operierte und eine nicht-operierte Gruppe eingeteilt. Das Gesamtüberleben (Overall Survival, OS) wurde berechnet und zur statistischen Auswertung Kaplan-Meier-Kurven mit Log-Rank-Test sowie univariate Cox-Proportional-Hazards-Modelle eingesetzt. Die Stadieneinteilung erfolgte nach den FIGO-Leitlinien von 2009.

Resultate: Insgesamt wurden 79 Patientinnen eingeschlossen (26 operierte, 53 nicht operierte). In der FIGO IV-Kohorte zeigte sich ein deutlicher Trend zu verbessertem Gesamtüberleben nach Operation (med. ÜL 159 vs. 6.0 Monate bei nicht-operierten; $p = 0.091$). Höherer BMI war der einzige signifikante präoperative Prädiktor für erhöhtes Sterberisiko (HR = 1,25; $p = 0.039$). Auch in der Rezidivkohorte war ein längeres Überleben nach Operation erkennbar (34.0 vs. 17.0 Monate; $p = 0.105$). Eine R0-Resektion war der einzige signifikante Prädiktor für verbessertes OS in der Rezidivkohorte (Log-Rank $p = 0.040$; Cox $p = 0.040$) und zeigte einen Trend in der FIGO IV-Gruppe (Log-Rank $p = 0.055$; Cox $p = 0.063$). Unerwartet war in der Rezidiv-Kohorte die Assoziation zwischen dem Fehlen einer Radiotherapie und besserem Überleben (Log-Rank $p = 0.044$), vermutlich bedingt durch Selektionsbias. Andere Faktoren, einschließlich des Operationszugangs oder adjuvanter Therapien, zeigten keine signifikanten Zusammenhänge mit dem Überleben, was hauptsächlich auf kleine Fallzahlen und statistische Unsicherheit zurückzuführen ist.

Conclusio: Die Studie bestätigt, dass eine vollständige Tumordebulking-Strategie (R0) entscheidend für ein verbessertes Gesamtüberleben ist. Trotz limitierter Fallzahlen unterstützen die beobachteten Trends bestehende Empfehlungen zur maximalen Debulking-Chirurgie und unterstreichen die Bedeutung einer sorgfältigen interdisziplinären Patientenauswahl.

Abstract

Objective: This study aimed to evaluate the role of cytoreductive surgery and survival determinants in patients with a first diagnosis of Stage IV endometrial carcinoma or recurrence, aligning with the planned AGO/ENGOT study "Evaluation of preoperative clinical and translational selection criteria for cytoreductive surgery in endometrial cancer".

Methods: This was a retrospective study of patients with advanced (FIGO IV) or recurrent endometrial cancer diagnosed and treated at LKH Graz between 2011 and 2020. Patients were grouped by surgical vs. non-surgical management. Overall survival (OS) was calculated, and statistical analyses included Kaplan-Meier curves with log-rank tests and univariate Cox proportional hazards models to assess the impact of surgery and related factors on survival. FIGO 2009 guidelines were used for staging.

Results: A total of 79 patients were included (26 surgical, 53 non-surgical). In the FIGO IV cohort, surgical treatment showed a strong numerical trend towards improved overall survival (median OS 159 months vs. 6.0 months for non-operated patients; $p = 0.091$). Body Mass Index (BMI) was the only significant preoperative predictor, with higher BMI linked to increased mortality risk ($HR = 1.25$, $p = 0.039$). For the recurrent disease cohort, surgery also trended towards longer survival (median OS 34.0 months vs. 17.0 months for non-operated patients; $p = 0.105$). Complete tumor removal (R0 resection) was the sole statistically significant predictor of improved survival in the recurrent cohort (log-rank $p = 0.040$, Cox overall model $p = 0.040$). A strong trend for R0 resection was also observed in the FIGO IV cohort (log-rank $p = 0.055$, Cox $p = 0.063$). A counterintuitive finding in the recurrent cohort was the statistically significant association between the absence of radiotherapy and better survival (log-rank $p = 0.044$), likely due to selection bias. Other factors, including surgical approach or adjuvant therapies, showed no statistically significant associations with survival, primarily due to small sample sizes and statistical instability.

Conclusion: This study confirms the important role of cytoreductive surgery in advanced and recurrent endometrial cancer management. Achieving complete macroscopic tumor removal (R0 resection) is crucial for improved overall survival, particularly in recurrent disease. While limitations due to small sample sizes exist, observed trends support existing literature emphasizing maximal debulking. Careful patient selection by multidisciplinary teams is essential to identify those most likely to benefit from radical surgical intervention.

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Abbreviations and definitions

BMI	Body Mass Index
CI	Confidence interval
dMMR	Deficient mismatch repair
EC	Endometrial cancer
ENGOT	European Network of Gynaecological Oncological Trial Groups
ESGO	European Society of Gynaecological Oncology
ESMO	European Society for Medical Oncology
ESP	European Society of Pathology
ESTRO	European Society for Radiotherapy and Oncology
FDA	Food and Drug Administration
FIGO	International Federation of Gynecology and Obstetrics
HR	Hazard ratio
LVSI	Lymphovascular Space Invasion
M	Mean
Mdn	Median
MIS	Minimally Invasive Surgery
MSI	Microsatellite instability
MSI-H	High level of microsatellite instability
MSS	Microsatellite stable
NSMP	No Specific Molecular Profile
OS	Overall survival
p53abn	p53-Abnormality
PFS	Progression-free survival
pMMR	Proficient mismatch repair system
POLEmut	POLE-Mutation
SCNA	Somatic Copy-Number Alterations
SD	Standard deviation
SE	Standard error
TCGA	The Cancer Genome Atlas
WHO	World Health Organization

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1. Introduction:

Endometrial cancer is the sixth most common cancer in women worldwide, with approximately 420.000 new cases and 97.000 deaths reported in 2022. (1) Since endometrial cancer presents with postmenopausal bleeding, it is detected early, making the early stage the most common form and resulting in a favorable prognosis with a five-year survival rate of 96%. However, in the uncommon case where a patient presents with advanced stage disease, 10-15% of all newly diagnosed cases (2), the five-year survival rate falls to around 20%. (3)

The risk of relapse is approximately 10-15% in early-stage disease, but it rises to 40-70% in advanced FIGO stages. Most recurrences occur within the first three years of follow-up, and the median survival of patients with recurrent endometrial cancer enrolled in clinical trials rarely surpasses 12 months. (4)

The primary treatment approach for endometrial cancer is total hysterectomy combined with bilateral salpingo-oophorectomy. (5) The optimal management of advanced endometrial cancer (FIGO IV) with distant metastases and recurrence is not well established. Chemotherapy and immunotherapy are standard therapeutic options, whereas the benefit of extensive surgery is uncertain in some cases.

1.1. FIGO staging:

The FIGO classification, developed by the International Federation of Gynecology and Obstetrics (FIGO), is a globally recognized system for staging gynecological cancers. It assesses tumor spread and progression in female reproductive organs, providing a standardized basis for diagnosis, treatment planning, and prognosis evaluation.

According to the FIGO staging system, complete staging involves hysterectomy and bilateral salpingo-oophorectomy and may also include pelvic and para-aortic lymph node dissection. (6)

The updated 2023 FIGO staging reflects the advances in pathology, molecular findings, and clinical outcomes since 2009. It includes the various histological types, tumor patterns, and molecular classification with the aim of better defining prognostic groups and creating substages to provide a more evidence-based context for treatment recommendations, which is why the performance of a complete molecular classification surrogate (POLEmut, MMRd, NSMP, p53abn) is encouraged in all cases of endometrial carcinoma. (7) It is important to note that molecular classification is not mandatory in the 2023 FIGO system. Two options are provided: one with molecular classification and one without. Both options offer improved prognostication based on the integrated new knowledge of anatomical and histopathological parameters, as well as molecular subtypes, when available. The molecular subtype should be recorded, if known, by adding an "m" (for molecular subtype) after the regular FIGO stage (based on anatomical and histopathological parameters). For example, for a low-grade (G2) endometrioid carcinoma with >50% myometrial invasion that is MMR deficient (MMRd), it would be noted as 2023 FIGO stage Ibm MMRd. (8)

The updated endometrial cancer staging system includes the following changes:

- Stage I:
  - (IA1) Non-aggressive histological types limited to an endometrial polyp or confined to the endometrium.
  - (IA2) Non-aggressive histological types involving less than half the myometrium with no or focal LVSI, based on WHO criteria.
  - (IA3) Low-grade endometrioid carcinomas limited to the uterus with simultaneous low-grade endometrioid ovarian involvement.
  - (IB) Non-aggressive histological types involving half or more of the myometrium with no or focal LVSI.
  - (IC) Aggressive histological types limited to a polyp or confined to the endometrium.
- Stage II:
  - (IIA) Tumors infiltrating the endocervical stroma.
  - (IIB) Tumors with substantial LVSI.
  - (IIC) Aggressive histological types (e.g., serous, clear cell, carcinosarcomas, undifferentiated, mixed, gastrointestinal-type mucinous endometrial carcinoma, mesonephric-like carcinomas) with any myometrial invasion.
- Stage III:
  - (IIIA1) Adnexal involvement
  - (IIIA2) Uterine serosa involvement
  - (IIIB1) Vaginal and/or parametrial involvement
  - (IIIB2) Pelvic peritoneal carcinomatosis

- Refinements in Stage IIIC to specify the extent of pelvic and abdominal lymph node metastases, with (IIIC1i) micrometastasis and (IIIC2ii) macrometastasis.

- Stage IV:
  - (IVA) Locally infiltrative disease.
  - (IVB) Extrapelvic peritoneal metastasis.
  - (IVC) Distant metastatic disease. (7)

Tables 1 and 2 provide an overview of the FIGO 2009 and FIGO 2023 staging. Adapted from Gaffney et al. (8)

Table 1: 2009 FIGO Staging

Stage		
I*		**Tumor confined to the corpus uteri**
IA*		No or less than half myometrial invasion
IB*		Invasion equal to more than half of the myometrium
II*		**Tumor invades cervical stroma, but does not extend beyond the uterus****
III*		**Local and/or regional spread of the tumor**
IIIA*		Tumor invades the serosa of the corpus uteri and/or adnexae#
IIIB*		Vaginal and/or parametrial involvement#
IIIC*		Metastases to pelvic and/or para-aortic lymph nodes#
	IIIC1*	Positive pelvic nodes
	IIIC2*	Positive para-aortic lymph nodes with or without positive pelvic lymph nodes
IV*		**Tumor invades bladder and/or bowel mucosa, and/or distant metastases**
IVA*		Tumor invasion of bladder and/or bowel muscosa
IVB*		Distant metastases, including intra-abdominal metastases and/or inguinal lymph nodes

Table 2: 2023 FIGO Staging

Stage		
I		**Confined to uterine corpus**
IA		Stage IAmPOLEm: POLEmut confined to uterine corpus +/− cervical invasion, regardless of LVSI or histotype
	IA1	Low-grade endometrioid, limited to polyp/endometrium (no myoinvasion)
	IA2	Low-grade endometrioid, myoinvasion <50%, no/focal LVSI
	IA3	Low-grade endometrioid carcinoma of the endometrium & ovary[#]
IB		Low-grade endometrioid, myoinvasion ≥50%, no/focal LVSI
IC		Aggressive histologies, limited to polyp/endometrium
II		Confined to the uterus
IIA		Low-grade endometrioid, invasion of the cervical stroma
IIB		Low-grade endometrioid, substantial LVSI
IIC		Aggressive histologies, myoinvasion
		Stage IICmp53abn: p53abn confined to uterus +/− cervical invasion + myoinvasion, regardless of LVSI or histotype
III		Local and/or regional spread
IIIA	IIIA1	Spread to ovary or fallopian tube (except when meeting stage IA3 criteria)
	IIIA2	Involvement of uterine subserosa or spread through the uterine serosa
IIIB	IIIB1	Metastasis or direct spread to the vagina and/or the parametria
	IIIB2	Metastasis to the pelvic peritoneum
IIIC	IIIC1	Pelvic lymph node metastasis
	IIIC1i	Micrometastasis (0.2-2mm and/or >200cells)
	IIIC1ii	Macrometastasis (>2mm in size)
	IIIC2	Para-aortic lymph node metastasis (up to renal vessels)
	IIIC2i	Micrometastasis (0.2-2mm and/or >200cells)
	IIIC2ii	Macrometastasis (>2mm in size)
IV		Advanced or metastatic disease

IVA	Invasion of the bladder mucosa and/or the intestinal mucosa
IVB	Peritoneal metastasis beyond the pelvis
IVC	Distant metastasis

*Either G1, G2, or G3.
**Endocervical glandular involvement only should be considered as Stage I and not as Stage II.
#Positive cytology has to be reported separately without changing the stage.
Some definitions:
Aggressive histotypes are composed of high-grade endometrioid (grade 3), serous, clear cell, undifferentiated, mixed, mesonephric-like, gastrointestinal mucinous type carcinomas, and carcinosarcomas.
LVSI: extensive/substantial, ≥5 vessels involved.
#myoinvasion <50% + no/focal LVSI + ovarian tumor pT1a. macrometastases are >2mm in size, micrometastases are 0.2-2mm and/or >200cells, a.

The major changes are:

1.1.1. LVSI in endometrioid EC

According to the 2023 FIGO staging, IA and IB stages include low-grade endometrioid endometrial cancers with no or only focal LVSI (Lymphovascular Space Invasion), while cases with substantial LVSI, as defined by the WHO criteria (five or more foci), are automatically classified as stage IIB, even if the tumor is confined to the uterus. Extensive research has highlighted LVSI as a key prognostic factor, including Bosse et al. (2018), who stated that substantial LVSI, unlike focal or absent LVSI, is the most significant independent predictor of pelvic recurrence, distant metastasis, and overall survival. They recommended basing therapeutic decisions on the presence of substantial LVSI, not "any" LVSI. (8, 9)

1.1.2. Histological subtypes

The 2023 FIGO staging system takes into account the significantly different prognoses of high-grade (aggressive) histological subtypes compared to low-grade (G1/G2) endometrioid (non-aggressive) subtypes. High-grade, aggressive subtypes with myometrial invasion are now classified as FIGO IIC, which includes serous, clear cell, high-grade endometrioid, mesonephric-like, gastrointestinal-type mucinous, undifferentiated carcinomas, and carcinosarcomas. (8)

A validation study by Schwameis et al. (2023), based on data from three ESGO-accredited centers, showed that patients with high-grade EC and myometrial invasion (2023 FIGO IIC) have a 5-year progression-free survival rate similar to the old FIGO stage II and new overall stage II patients but a lower overall survival rate compared to low-grade EC. (10)

1.1.3. New molecularly defined FIGO stages $IAm_{POLEmut}$ and $IICm_{p53abn}$

Studies have shown that molecular subtypes majorly impact prognosis, often making anatomical borders less relevant. (11, 12) New evidence is emerging that highlights the predictive value of these molecular subtypes, which are already guiding treatment decisions and will continue to do so.

As molecular subtypes significantly influence outcomes, the 2023 FIGO staging system has been updated to incorporate these subtypes with two molecularly defined substages for early-stage disease:

- Uterus-confined disease with a POLE mutation (2023 FIGO IAm POLEmut)
- Uterus-confined disease with myometrial invasion and a p53 abnormality (2023 FIGO IICm p53abn)

These changes offer a more accurate prediction of progression-free survival (PFS) and overall survival (OS). For example, a study of 75 stage I, grade 3 (FIGO 2009) patients showed a 95.8% 3-year progression-free survival (PFS) for the POLE mutation group compared to 60% for the p53 mutated group. (12)

The new system allows for better prognostication and treatment decision-making based on molecular classifications. POLEmut cases typically have a good prognosis even without adjuvant treatment, while p53 abnormal cases with myometrial invasion show poor outcomes and benefit from chemotherapy. (8)

1.1.4. Disaggregation of 2009 FIGO stage IIIA to new 2023 FIGO stages IA3 and IIIA1

Previously, the 2009 FIGO system classified all ovarian metastases of endometrial cancer (EC) as stage IIIA. The 2023 FIGO system now differentiates between:

- Low-grade endometrioid carcinomas of the endometrium with ovarian involvement (classified as FIGO IA3, if specific criteria are met)
- Other ovarian metastatic patterns (remain classified as FIGO IIIA1)

This distinction is based on the favorable prognosis of low-grade endometrioid carcinoma in both locations when criteria such as <50% myometrial invasion, absence of LVSI, and no other metastases are met (according to the World Health Organization (WHO)). (13) Additionally, the ESGO-ESTRO-ESP guidelines specify that the ovarian tumor must correspond to pT1a.

Studies have shown these tumors are clonally related, confirming they are true metastases rather than separate primary tumors. This differentiation is crucial for treatment decisions, as ESGO-ESTRO-ESP guidelines do not recommend adjuvant therapy for these cases. (8, 14-16)

1.1.5. Refinement of lymph node metastasis - new 2023 FIGO stages IIIC1i/ii and IIIC2i/ii

The updated 2023 FIGO stage distinguishes between micro- and macrometastases in pelvic (IIIC1) and para-aortic (IIIC2) lymph node metastases by adding "i" for micro and "ii" for macrometastases. Similar to other staging systems, the size of nodal metastases significantly impacts patient prognosis, with pelvic and para-aortic lymph node metastases indicating a poorer prognosis compared to micrometastatic lymph node disease ($p = 0.041$). (8, 17)

1.1.6. Disaggregation of 2009 FIGO stage IVB to new 2023 FIGO stages IIIB, IVB and IVC

The previous 2009 FIGO stage IVB included a heterogeneous group of patients by clustering all cases of peritoneal carcinomatosis (whether pelvic or extrapelvic), organ-specific distant metastases, and lymph node metastases beyond the pelvic and para-aortic regions into a single category.

In the updated 2023 FIGO staging system, peritoneal carcinomatosis has been distinguished from distant metastases. Peritoneal carcinomatosis confined to the pelvis has been reclassified as stage IIIB2 (previously part of 2009 stage IVB), while peritoneal carcinomatosis extending beyond the pelvis remains within stage IV but has been assigned a separate substage (2023 stage IVB), differentiating it from other distant intra- and extra-abdominal metastases (now classified as stage IVC). (8)

A 2020 SEER Database study of over 900 patients with 2009 stage IVB disease demonstrated that prognosis varied significantly depending on the site of metastasis. Patients with peritoneal spread had considerably better survival outcomes than those with organ-specific metastases. (18)

A National Cancer Database analysis of over 130,000 patients supports these findings, showing a ten-year overall survival of 49.4% for 2023 FIGO stage IIIB2 compared to 18.7% for 2009 stage IVB.

This refined classification of the previously heterogeneous 2009 FIGO stage IV disease has significant clinical implications. Treatment decisions, particularly regarding surgical versus non-surgical first-line approaches and the extent and type of surgery, differ considerably between cases with limited pelvic versus extensive/extrapelvic peritoneal carcinomatosis. (8)

1.1.7. Molecular Classification:

Recent therapeutic approaches are increasingly guided by molecular classification. In addition to the traditional Bokhman classification into Type I and Type II tumors, based on clinical, metabolic, and endocrine characteristics (table 3) (19)**,** and the histopathological classification by WHO (e.g., endometrioid, serous, or clear-cell adenocarcinoma) (figure 1) (20), a new classification system has emerged that incorporates molecular features, providing a more comprehensive framework for understanding tumor biology and guiding personalized treatment strategies.

TCGA ("The Cancer Genome Atlas") Molecular Classification classifies endometrial cancer in 4 categories:

- **POLE mutation:** This subclass is characterized by somatic inactivating hotspot mutations in the exonuclease domain of the POLE gene and a very high mutational burden (ultramutated). Regardless of grade, they usually have an excellent prognosis.
- **Microsatellite instability (MSI):** This subclass is characterized by a high number of microsatellite alterations and exhibits an intermediate prognosis.
- **Copy-number-low (CN-low):** This group has low somatic copy-number alterations (SCNA-low) and low mutational burden. Estrogen receptor expression and histological grade impact the prognosis in this intermediate group.
- **Copy-number-high (CN-high):** These tumors are defined by a high number of SCNA (SCNA-high), nearly universal (95%) TP53 mutations, and a highly unfavorable prognosis. (7)

The p53 status is currently the most important criterion for distinguishing between favorable and unfavorable prognoses. The p53abn subtype is particularly aggressive with a high proliferative potential, and at the time of initial diagnosis, the tumor is often already at an advanced stage, frequently with metastases. This highlights the importance of p53 assessment during the initial diagnosis. (21)

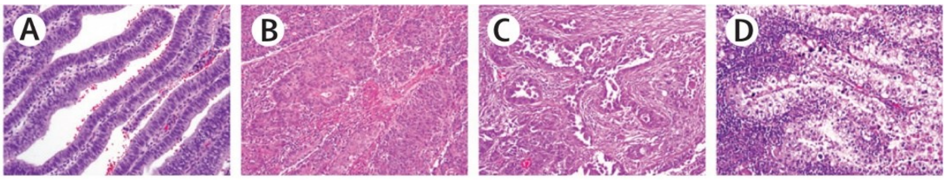
Additionally, about 5% of patients with endometrial cancer have more than one molecular subtype (known as multiple classifiers), which is why testing for all relevant molecular markers is crucial. Based on current knowledge, if a POLE mutation is present, it is the strongest predictor of prognosis. However, if both dMMR and p53 mutations are found, dMMR takes priority in guiding prognosis. (21)

Molecular subtyping is not only important for prognosis but also influences treatment decisions, particularly in determining the use of immuno-oncological therapies. About one-third of all endometrial cancers show dMMR/MSI-H, with up to 5% of these cases linked to Lynch syndrome. For patients with advanced endometrial cancer and dMMR/MSI-H, immunotherapy has emerged as a promising new treatment option. (21)

Table 3: Bokhman classification: Type I vs. Type II endometrial tumors by clinical, metabolic, and endocrine features (19, 20)

	Type I	**Type II**
Distribution	60-70%	30-40%
Reproductive function	Decreased	No disturbances
Onset of menopause	After age 50 years	Younger than age 50 years
Background endometrium	Hyperplasia	Atrophy
Oestrogen associated	Yes	No
Associated obesity, hyperlipidaemia, and diabetes mellitus	Yes	No
Tumour grade	Low (grades 1-2)	High (grade 3)
Myometrial invasion	Superficial	Deep
Potential for lymphogenic metastatic spread	Low	High
Prognosis	Favourable	Unfavourable
Sensitivity to progestagens	High	Low
Outcome (5-year survival)	86%	59%

Figure 1: Common epithelial endometrial carcinomas: clinical, pathological, and molecular characteristics (20)



Histological type	Endometrioid	Endometrioid	Serous	Clear cell
Histological grade	Low	High	High	High
Metastasis	Uncommon	Lymph nodes Distant organs	Lymph nodes Peritoneal Distant organs	Lymph nodes Peritoneal –/+
Prognosis	Favourable	Poor	Poor*	Poor*†
Molecular markers[18–21]				
ER/PR expression	+	+/–	–/+	–
PTEN expression	–/+	–/+	+	+
DNA MMR loss	–/+	–/+	–	–/+
Aberrant P53	–	–/+	+	–/+
Ki-67/MIB-1	Low	High	High	Low or high

1.2. Immunotherapy

In cases of advanced or recurrent endometrial cancer, surgery and radiotherapy alone are often insufficient for achieving long-term disease control, making systemic therapy essential. Until now, the standard first-line treatment for patients with advanced EC consisted of carboplatin and paclitaxel chemotherapy, sometimes combined with radiotherapy. However, this approach had limited long-term effectiveness, with a median overall survival (OS) of less than three years.

Advances in understanding the molecular characteristics of advanced and recurrent endometrial cancer have paved the way for new targeted treatment approaches that significantly improve survival outcomes, particularly with the introduction of immune checkpoint inhibitors. These therapies harness the body's immune system to fight cancer by blocking the PD-1 receptor on immune cells (mainly T cells) and tumor cells, allowing the immune system to better recognize and attack the tumor.

Given these developments, biomarker testing at the time of initial diagnosis is a key recommendation in the guidelines of ESGO, ESTRO, and ESP, as well as the ESMO Clinical Practice Guidelines and the German S3 guidelines. If not done initially, biomarker assessment should be performed upon recurrence or metastasis, as it plays a critical role in guiding therapeutic decisions at that stage. (21, 22)

Immunotherapy in EC with microsatellite high/deficient mismatch repair system (MSI-H/dMMR):

Approximately 17-36% of patients with endometrial cancer have tumors with deficient mismatch repair (dMMR), including both epigenetic and probable genetic causes. These patients are more likely to have advanced-stage, high-grade tumors with poor prognostic features like lymphovascular space invasion. Especially in advanced stages (FIGO III/IV), recurrence rates are significantly higher in those with epigenetic dMMR compared to those with proficient MMR (48% vs 3.4%), despite similar adjuvant treatment, suggesting that the underlying tumor biology - rather than treatment strategy - is a key determinant of prognosis. However, dMMR tumors respond particularly well to immunotherapy due to their high mutation rates and neoantigen load. (23) Activated CD3/8-positive tumor-infiltrating lymphocytes can induce PD-L1 expression in cancer cells and other cell types. Anti-PD-1 antibodies (pembrolizumab, nivolumab, and dostarlimab) and anti-PD-L1 antibodies (atezolizumab and durvalumab) target key immune checkpoint pathways that tumors use to evade the immune system. PD-1, found on activated T cells, normally binds to PD-L1 or PD-L2 on tumor or immune cells, which dampens the immune response. Anti-PD-1 antibodies prevent this by targeting PD-1 on T cells, while anti-PD-L1 antibodies block PD-L1 on tumor or immune cells. Both approaches help keep T cells active and support an effective antitumor response. (24)

Dostarlimab and pembrolizumab have shown strong efficacy. The latter has been approved by the FDA (Food and Drug Administration) for the treatment of patients with recurrent dMMR endometrial cancer who have progressed on prior therapies. In a pivotal phase II trial, 57% of patients with MSI-H tumors responded to pembrolizumab, with a median progression-free survival of 27 months. Similarly, dostarlimab showed a 42% response rate with long-lasting effects, and most patients continued to benefit by the time of reporting. (23, 24)

Other immunotherapies, such as avelumab and durvalumab (anti-PD-L1 antibodies), have also shown promising efficacy in the dMMR population. Yarchoan and colleagues showed that, across all cancer types, dMMR tumors respond to PD-1/PD-L1 immunotherapies better than even traditionally “immune-sensitive” cancers like melanoma and lung cancer. (23, 24)

Building on these successes, several large randomized phase III trials (RUBY, NRG-GY018, AtTEnd, and DUO-E) have evaluated the addition of immune checkpoint inhibitors to standard first-line chemotherapy (carboplatin and paclitaxel) in advanced or recurrent endometrial cancer. In all studies, patients with dMMR tumors showed substantial benefit from the addition of immunotherapy. For example, in the RUBY trial, adding dostarlimab to chemotherapy reduced the risk of progression or death by 72% (HR 0.28) and improved overall survival (OS) by 68% (HR 0.32) in the dMMR subgroup. Similarly, the NRG-GY018 trial demonstrated a hazard ratio for PFS of 0.30 in dMMR patients treated with pembrolizumab plus chemotherapy versus chemotherapy alone. These consistent findings have solidified chemo-immunotherapy as the new standard of care for patients with dMMR/MSI-H endometrial cancer(25). The FDA has recently approved three new treatment options:

- Durvalumab (Imfinzi) was approved for use with chemotherapy in patients with dMMR.
- Pembrolizumab (Keytruda) received approval for use with chemotherapy regardless of dMMR status, expanding its use beyond dMMR-only patients.
- Dostarlimab (Jemperli) was approved in combination with chemotherapy and regardless of dMMR status. (It had previously been approved in 2023 as a monotherapy for dMMR tumors.) (26)

<u>Immunotherapy in EC with microsatellite stable or proficient mismatch repair system (MSS/pMMR):</u>

About 30% of endometrial cancer patients have tumors with a high level of microsatellite instability (MSI-H), which makes them especially responsive to immunotherapy. But the majority (around 70%) have microsatellite stable (MSS) tumors, which don’t respond well to current immune checkpoint inhibitors. In the KEYNOTE-028 trial, pembrolizumab was administered to 24 patients with recurrent endometrial cancer who had already undergone at least two prior lines of chemotherapy and showed PD-L1 positivity. The majority of these patients had proficient mismatch repair (pMMR) status. The treatment led to an overall response rate of 13%, with 13% of patients achieving stable disease.

To improve outcomes for these patients, researchers began testing new combination therapies. One promising strategy is to pair immunotherapy with drugs that block blood vessel growth in tumors (antiangiogenics). This approach was tested in the KEYNOTE-146 trial, where pembrolizumab was combined with lenvatinib, a multikinase inhibitor against vascular endothelial growth factor receptors 1, 2, and 3 in patients with advanced endometrial cancer. Nearly 40% of patients responded to the combination, which led to accelerated FDA approval for this treatment in advanced endometrial cancer, even in patients without MSI-H.

The follow-up KEYNOTE-775 phase III trial confirmed these results. It included over 800 patients with advanced or recurrent endometrial cancer who had already tried chemotherapy. Compared to standard chemotherapy, the pembrolizumab/lenvatinib combination significantly extended both progression-free and overall survival. It also had a higher response rate (32%) compared to 15% with standard chemo.

However, the downside is the high rate of side effects. Nearly 89% of patients being treated with the chemotherapy-combination experienced serious side effects, leading many to stop treatment early. Because of this, researchers are now exploring other, possibly gentler combinations.

One such option is combining atezolizumab (another immunotherapy) with bevacizumab (a VEGF inhibitor). Early results from a smaller study looked promising: a 33% response rate, with many patients doing well for over a year. Importantly, this combo might come with fewer side effects than pembrolizumab/lenvatinib. These findings still need to be confirmed in larger trials, but they offer hope for more effective and tolerable options for women with MSS endometrial cancer. (23, 24)

2. Material and Methods

2.1. Study Objective and Design

This study relies on a retrospective data analysis. The research question is based on the planned AGO/ENGOT study "Evaluation of preoperative clinical and translational selection criteria for cytoreductive surgery in endometrial cancer." This planned multicenter retrospective descriptive study aims to evaluate prognostic factors predicting the benefit of cytoreductive surgery in advanced or recurrent endometrial cancer and identify prognostic markers for the clinical outcome.

2.2. Study population

The patients were selected from the data acquisition system openMEDOCS of LKH Graz. The eligibility criteria included the following: Patients aged ≥ 18 years with

(1) a first diagnosis of advanced endometrial carcinoma (FIGO IV) or
(2) recurrence,

between January 2011 and December 2020.

Patients were divided into two groups according to their treatment: a surgical and non-surgical group. Within these groups, patients with advanced-stage carcinoma were compared to patients with recurrent disease.

2.3. Data Source and Collection

Individual patient data were collected from electronic database of LKH Graz, including inpatient charts, operative reports, pathology records, discharge summaries, outpatient records.

The recorded data included the age at diagnosis, BMI, grading, staging (TNM-classification, FIGO classification), histology, metastasis, type of surgery, non-surgical therapy, and months of survival. Overall survival (OS) was calculated from the date of initial diagnosis of FIGO IV or recurrent carcinoma until death or the last follow-up.

All extracted data were systematically entered into a structured Excel spreadsheet. Each variable was coded according to a predefined coding scheme to ensure consistency. For example, for the variable "type of surgery", the following coding was applied: 0 = no surgery, 1 = laparoscopic surgery, 2 = vaginal surgery, 3 = open abdominal surgery. Other variables were also standardized: for example, resection status was coded as 0 = R0 and 1 = R1, binary treatment variables such as chemotherapy or radiotherapy were recorded as 1 = yes and 0 = no, and missing values were marked accordingly.

The Excel dataset was then imported into IBM SPSS Statistics (Version 30.0.0.0) for statistical analysis. The dataset was reviewed for completeness and logical consistency. Missing data were handled using the pairwise deletion method. This approach allowed the inclusion of all available data for each specific analysis by excluding only those cases with missing values in the variables required for that particular test. As a result, the maximum number of valid cases was retained for each statistical procedure.

To verify the study's results against existing literature, an internet search (mostly PubMed) was conducted to identify studies reporting on the effect of cytoreduction for advance-staged and recurrent endometrial cancer on survival, in comparison with medical management, as well as studies reporting on characteristics of patients who received cytoreductive surgery.

The following table provides an overview of all variables included in the statistical analysis, along with the corresponding data format and coding schemes.

Table 4: Overview of Variables

Variable	Format	Example / Coding
Age at Diagnosis	Numeric (years)	e.g., 73
BMI	Numeric (kg/m^2)	e.g., 30.1
First Diagnosis Date	Numeric Date (MM/YYYY)	e.g., 01/2010
FIGO Stage	Roman numerals	e.g., IVa
TNM Classification	Text	e.g., pT2a, N0
Grading	Ordinal (G1-G4)	e.g., G1
Endometrial Type	Numeric	1 = Type I, 2 = Type II
Histological Status *	Numeric (coded)	e.g., 4 = clear cell carcinoma
Histological Status (text) *	Text	e.g., Clear cell carcinoma
Type of Surgery	Numeric	0 = None, 1 = Laparoscopic, 2 = Vaginal, 3 = Abdominal
Lymphadenectomy	Numeric (coded)	e.g., 2 = paraaortic
Chemotherapy	Binary	1 = Yes, - = No
Antihormonal Therapy	Binary	1 = Yes, - = No
Radiotherapy	Binary	1 = Yes, - = No
Resection Status	Text	R0, R1, - (unknown)
Metastasis	Binary	1 = Yes, - = No
Number of Recurrences	Numeric	e.g., 1
Date of First Recurrence	Numeric Date (MM/YYYY)	e.g., 01/2011
Time to First Recurrence (months)	Numeric	e.g., 15
Lymphatic Metastasis	Numeric (coded)	e.g., 1 = pelvic
Hematogenous Metastasis	Numeric (coded)	e.g., 1 = liver
Locoregional Metastasis	Numeric (coded)	e.g., 1 = vagina
Peritoneal (cavitational) Metastasis	Numeric (coded)	e.g., 0 = peritoneal
Date of Last Follow-Up or Death	Numeric Date (MM/YYYY)	e.g., 07/2022
Overall Survival	Numeric (months)	e.g., 25

*In cases where tumors exhibited multiple histological components, such as endometrioid adenocarcinoma with focal mucinous differentiation, all observed histological components were documented. For instance, in such a case, both the endometrioid and the mucinous components were recorded. As a result, the reported numbers do not reflect the number of tumors with a specific histology but rather the total number of occurrences of each histological component across all cases.

2.4. Ethics and Data Protection

The protocol was approved by the ethics committee of the Medical University of Graz.

As this is a retrospective data analysis, no new data were collected, and therefore informed consent from participants was not required. However, privacy and confidentiality of the data were ensured in accordance with ethical guidelines.

2.5. Study definitions and statistical analysis

The staging was based on FIGO 2009 guidelines.

SPSS Statistics (Version 30.0.0.0) was used for statistical analysis. As a first analytical step, descriptive statistics were performed to characterize the study population in terms of sociodemographic, clinical, and tumor-related variables.

For continuous variables such as age, body mass index (BMI), and overall survival time, the mean, standard deviation, median, minimum and maximum were calculated.

Categorical variables such as FIGO stage, tumor grade, histological subtype, resection status (R0 vs. R1), presence of metastases, and receipt of adjuvant chemotherapy or radiotherapy were summarized using absolute and relative frequencies (n, %).

A preliminary comparison between surgically and non-surgically treated patients was conducted based on these characteristics.

In order to evaluate prognostic factors predicting the benefit of cytoreductive surgery in advanced or recurrent endometrial cancer and identify prognostic markers for the clinical outcome, the analysis focused on the following objectives

1. <u>To determine whether surgery impacts overall survival</u>

   For each subgroup - patients with FIGO stage IV disease and patients with recurrent disease - overall survival was compared between those who underwent cytoreductive surgery and those who did not. Kaplan-Meier survival curves were generated and differences in survival distributions were assessed using the log-rank test ($p < 0.05$ deemed significant). Additionally, a univariate Cox proportional hazards model with surgery as the sole covariate was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) for the effect of surgery. Given the limited number of events in each subgroup, results from the Cox model were interpreted with caution.

2. <u>To understand the extent to which surgery influences survival</u>

   Subgroup analyses were performed separately for patients with FIGO stage IV disease and those with recurrent disease, with the aim of identifying clinical and treatment-related factors that modify survival among operated patients. Within each surgical subgroup, Kaplan-Meier survival curves were generated and compared using the log-rank test ($p < 0.05$ deemed significant). The following variables, each reflecting either the surgical procedure itself or its immediate clinical context, were analyzed individually:

- Surgical approach (laparotomy vs. laparoscopy)
- Extent of lymphadenectomy (none vs. sentinel vs. pelvic vs. pelvic + paraaortic)
- Resection status (R0 vs. R1)
- Adjuvant chemotherapy (yes vs. no)
- Adjuvant radiotherapy (yes vs. no)
- Adjuvant antihormonal therapy (yes vs. no)

To quantify each factor's effect on survival, univariate Cox proportional hazards models were then fitted separately for each variable, yielding hazard ratios (HR) with 95% confidence intervals. This two-step approach, consisting of a descriptive survival curve comparison followed by one at a time hazard estimation, ensures that only those factors directly related to the surgical intervention and its immediate oncologic context are assessed, while avoiding overfitting in subgroups with limited event counts.

Note: The analysis of the extent of lymphadenectomy applies only to the FIGO IV cohort. In the recurrent-disease group, lymphadenectomy at the time of recurrence was not assessed because all patients had already undergone nodal staging during their initial surgery.

3. <u>To identify which preoperative characteristics predict benefit from surgery</u>

In order to determine which patient-related factors available before surgery were associated with improved overall survival following cytoreductive surgery, univariate Cox proportional hazards models were fitted separately for each candidate variable in the operated cohort. The following preoperative characteristics were evaluated:

- Age (continuous; years)
- Body mass index (BMI) (continuous; kg/m²)
- FIGO Substage (ordinal; I, Ia, Ib,….., IVb)
- Tumor grade (ordinal; G1-G4)
- Histological subtype (nominal; endometrioid, serous, clear cell,..)
- Endometrial type (nominal; Type I, Type II)
- Presence of metastases at diagnosis (binary; yes vs. no)

In the recurrence cohort, the preoperative assessment additionally included parameters from the initial treatment of the primary tumor, as these reflect patient status prior to the surgical management of recurrence:

- Type of primary surgery (nominal; laparoscopic, abdominal, vaginal)
- Resection status of the primary tumor (binary; R0, R1)
- Extent of lymphadenectomy during initial surgery (nominal; none, sentinel, pelvic, pelvic + paraaortic)
- Adjuvant chemotherapy after primary diagnosis (binary; yes vs. no)
- Adjuvant antihormonal therapy after primary diagnosis (binary; yes vs. no)
- Adjuvant radiotherapy after primary diagnosis (binary; yes vs. no)

Multivariate modeling was not performed in this context because only six deaths occurred in the FIGO IV surgery group and five in the recurrence surgery group. Established recommendations require at least ten events per covariate to ensure reliable estimates; attempting multivariable analysis here would risk overfitting and unstable results. Consequently, only univariate models were conducted to ensure valid and interpretable results. For each variable, the model produced a hazard ratio (HR) and 95% confidence interval (CI). An HR below 1.0 was interpreted as a protective association (longer survival), while an HR above 1.0 indicated an increased risk of death.

This focused approach permits an exploratory assessment of preoperative predictors of surgical benefit without violating statistical assumptions.

Kaplan-Meier survival curves and other visual representations of the data were generated using IBM SPSS Statistics. Additional formatting of figures and tables was performed using Microsoft Excel.

3. Results:

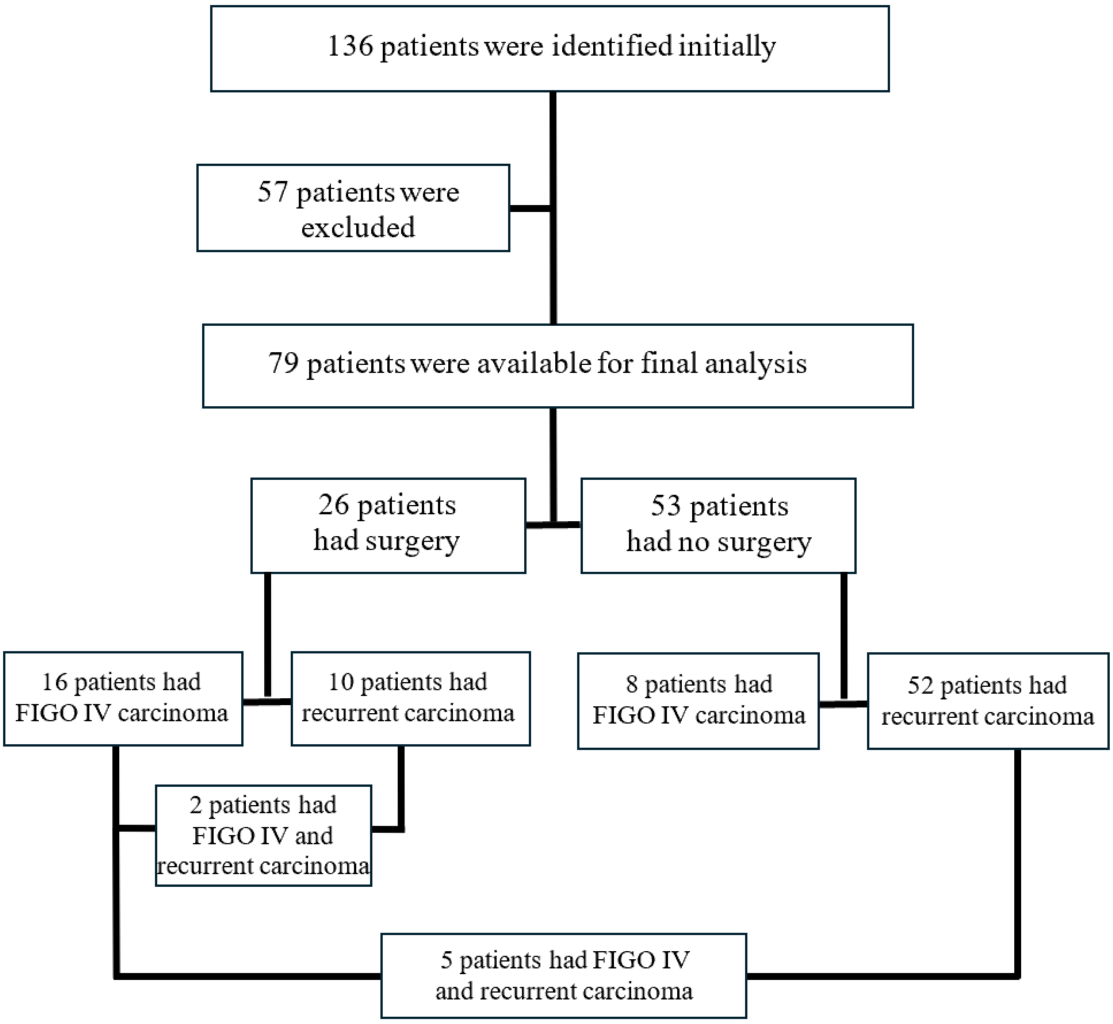
3.1. Patient characteristics:

A total of 136 records of potential interest were identified in the initial search of electronic databases. A total of 57 records were excluded, with the majority found to be the wrong population (other carcinoma, e.g. cervical cancer, sarcoma, etc.; no FIGO IV classification nor recurrence) or the timing of the diagnosis not overlapping with the period specified in the inclusion criteria.

Therefore, 79 patients were identified as meeting all inclusion criteria. Out of these, 26 patients underwent surgical treatment, including 16 patients with FIGO stage IV disease and 10 patients with recurrent carcinoma. Among the 53 patients who did not undergo surgery, eight were diagnosed with FIGO stage IV disease and 52 had recurrent disease. Notably, 7 patients presented with both FIGO stage IV and recurrence.

The patient selection flow chart is shown in Fig.2

Figure 2: Patient selection



The mean age of the study cohort was 66.57 years (Mdn = 67, SD = 10.63), ranging from 34 to 87 years. The mean BMI was 28.47 kg/m² (Mdn = 27.95, SD = 6.05), with values ranging from 16 to 43 kg/m². 62 patients had experienced at least one recurrence during their disease course.

Regarding histological subtypes, 45 patients were diagnosed with type I endometrial carcinoma, 5 with a mixed type I and II, 23 with type II, and in 6 patients the histological classification was unknown.

3.2. Subgroup Analyses

FIGO Stage IV + Surgery (n = 16):

Patients undergoing surgery in the FIGO IV subgroup had a mean age of 61.06 years (SD = 10.08) and a mean BMI of 27.04 kg/m² (SD = 5.15). The average overall survival in this group was 46.38 months (SD = 50.95). The majority had type II endometrial carcinoma (n = 8), while five had type I, and one patient had a mixed type I and II. The histological subtype was unknown in two cases.

Five patients underwent laparoscopic surgery and 11 underwent open abdominal surgery (68.8%), including five R0 resections. Lymphadenectomy was performed in 9 cases: sentinel nodes (n = 2), pelvic dissection (n = 2), and combined pelvic and paraaortic dissection (n = 5). Chemotherapy was administered to 10 patients, antihormonal therapy to one, and radiotherapy to six patients. Among those who experienced recurrence after primary FIGO IV diagnosis (n = 7), two underwent secondary abdominal surgery, three received chemotherapy, five received antihormonal therapy, and one received radiotherapy.

FIGO Stage IV + No Surgery (n = 8):

These patients were older, with a mean age of 72.75 (SD = 8.65) years. The mean BMI was 27.24 kg/m² (SD = 6.83) (one missing value). The average overall survival was 11 months. Five patients had type I cancer, two had type II, and one was unclassified.

Regarding therapy, only two patients received chemotherapy, three received antihormonal therapy, and one underwent radiotherapy.

Table 5: Clinicopathologic characteristics (FIGO IV cohort)

Characteristic	*Surgery (n = 16)*	*No Surgery (n = 8)*
Demographics		
Age, mean ± SD (years)	61.06 ± 10.08	72.75 ± 8.65
BMI, mean ± SD (kg/m²)	27.04 ± 5.15	27.24 ± 6.83 (1 missing)
Tumor Type		
Type I	5 (31.3%)	5 (62.5%)
Type II	8 (50.0%)	2 (25.0%)
Mixed I + II	1 (6.3%)	0
Unknown	2 (12.5%)	1 (12.5%)

Histology (detailed)*		
Unknown	1	1
Other histologic type	1	1
Endometrioid component	7	5
Serous component	4	2
Clear-cell component	2	1
Carcinosarcoma	2	0
Undifferentiated component	1	0
Surgical Details		N/A
Approach: Laparoscopic	5 (31.3%)	-
Approach: Laparotomy	11 (68.8%)	-
R0 resections	5 (31.3%)	-
Lymphadenectomy	9 (56.3%)	-
Sentinel node	2	-
Pelvic dissection	2	-
Pelvic + para-aortic	5	-
Adjuvant Therapy		
Chemotherapy	10 (62.5%)	2 (25.0%)
Antihormonal therapy	1 (6.3%)	3 (37.5%)
Radiotherapy	6 (37.5%)	1 (12.5%)
Recurrence treatment (n = 7)		N/A
Secondary surgery	2 (28.6%)	-
Chemotherapy	3 (42.9%)	-
Antihormonal therapy	5 (71.4%)	-
Radiotherapy	1 (14.3%)	-
OS, mean ± SD (months)		
All patients	46.38 ± 50.95	11.00 ± -
Censored patients (follow-up time)	51.20 ± 47.51	19.50 ± 21.95
Deceased patients (OS)	38.33 ± 60.01	2.50 ± 2.38

*All values for histological components are cumulative and based on tumors with multiple documented histologic subtypes. As a result, the reported numbers do not reflect the number of tumors with a specific histology but rather the total number of occurrences of each histological component across all cases. Percentages refer to the respective group sizes.

Recurrent Disease + Surgery (n = 10):

Patients in this subgroup had a mean age of 66.30 years (Mdn = 63.5, SD = 10.53) and a mean BMI of 22.61 kg/m² (Mdn = 21.95, SD = 2.91). The mean overall survival was 44.80 months (Mdn = 34.50, SD = 34.65). Tumor grades were G1 (n = 3), G2 (n = 2), and G3 (n = 5). Most patients had type I endometrial carcinoma (n = 7), while one had type II, one had mixed type I/II, and one was unknown.

Initial surgical treatment included laparoscopy (n = 3) and abdominal surgery (n = 7), with R0 resection achieved in seven cases. In one patient, sentinel lymph nodes were removed, one patient underwent a pelvic lymphadenectomy, and in three patients, both pelvic and para-aortic lymphadenectomy were performed. Three patients received chemotherapy, none received antihormonal therapy and three patients received radiotherapy.

At recurrence, five underwent abdominal surgery, and five had other procedures such as TURB or lobectomy. R0 resection was documented in three. Four received chemotherapy, two received antihormonal therapy, and four received radiotherapy. Five had lymphatic metastases (unspecified location, n = 1; paraaortic, n = 1; pelvic, n = 1; mediastinal, n = 2), six hematogenous spread (lung, n = 3; spleen, n = 1; bone, n = 2), three local-regional (vagina, n = 1; pelvis, n = 2), and two peritoneal involvement. Five patients developed a second recurrence; three were operated on (all R0), four received chemotherapy, three received antihormonal therapy, and two received radiotherapy.

Recurrent Disease + No Surgery (n = 52):

This subgroup had a mean age of 67.25 years (Mdn = 70, SD = 10.37) and a mean BMI of 29.86 kg/m² (Mdn = 29.15, SD = 5.75). The average overall survival in this group was 20.6 months (Mdn = 10.5, SD = 27.58). Grading included G1 (n = 10), G2 (n = 15), G3 (n = 22), and unknown (n = 5). Most patients had type I endometrial carcinoma (n = 31), four had mixed type I/II, 14 had type II, and in three cases the type was unknown.

Surgical treatment at initial diagnosis of the primary carcinoma included laparoscopic (n = 24), vaginal (n = 5), and abdominal approaches (n = 22); one patient did not undergo surgery. R0 resection was achieved in 35 patients. Sentinel node biopsy (n = 10, including 1 patient who also underwent pelvic lymphadenectomy), pelvic (n = 11), and combined pelvic and paraaortic lymphadenectomy (n = 12) were performed. Adjuvant therapies included chemotherapy (n = 20), antihormonal therapy (n = 2), and radiotherapy (n = 35). At recurrence, 23 received chemotherapy, 31 antihormonal therapy, and 15 radiotherapy. Lymphatic metastases were documented in 23 patients (unspecified location, n = 13; paraaortic, n = 10; inguinal, n = 3; mediastinal, n = 2), hematogenous metastases in 23 patients (unspecified, n = 4; liver, n = 9; lung, n = 11; spleen, n = 1; bone, n = 12; kidney, n = 2; brain, n = 2), locoregional metastases in 30 patients (unspecified, n = 2; vagina, n = 5; pelvis, n = 17; vagina and pelvis, n = 6), and peritoneal metastases in 12 patients. Three patients developed a second recurrence and were treated without surgery.

Table 6: Clinicopathologic characteristics (Recurrence cohort)

Characteristic	***Surgery (n = 10)***	***No Surgery (n = 52)***
Demographics		
Age, mean ± SD (median)	66.30 ± 10.53	67.25 ± 10.37
BMI, mean ± SD (median)	22.61 ± 2.91	29.86 ± 5.75 (1 missing)
Tumor Type		
Type I	7 (70.0%)	31 (59.6%)
Type II	1 (10.0%)	14 (26.9%)
Mixed I + II	1 (10.0%)	4 (7.7%)
Unknown	1 (10.0%)	3 (5.8%)
Tumor Grade		
G1	3	10
G2	2	15
G3	5	22
Unknown	-	5
Histological components		
Unknown	1	3
Other histologic type	-	1
Endometrioid component	8	33
Serous component	2	11

Clear-cell component	1	6
Mucinous component	-	3
Carcinosarcoma	-	2
Undifferentiated	-	1
Surgical Details (initial)		
Approach: Laparoscopic	3 (30.0%)	24 (46.2%)
Approach: Laparotomy	7 (70.0%)	22 (42.3%)
Approach: Vaginal	-	5 (9.6%)
No initial surgery	-	1 (1.9%)
R0 resection	7 (70.0%)	35 (67.3%)
Lymphadenectomy (initial)		
Sentinel node	1	10 (incl. 1 with pelvic)
Pelvic dissection	1	11
Pelvic + para-aortic dissection	3	12
Adjuvant treatment (initial)		
Chemotherapy	3 (30.0%)	20 (38.5%)
Antihormonal therapy	0	2 (3.8%)
Radiotherapy	3 (30.0%)	35(67.3%)
Time from initial diagnosis to first recurrence, mean ± SD (months)	56.00 ± 54.23	34.19 ± 42.55
Recurrence treatment		
Surgery (abdominal)	5 (50.0%)	-
Other procedures (TURB, lobectomy)	5 (50.0%)	-
R0 resection	3 (30.0%)	-
Chemotherapy	4 (40.0%)	23 (44.2%)
Antihormonal therapy	2 (20.0%)	31 (59.6%)
Radiotherapy	4 (40.0%)	15 (28.8%)
Metastasis at recurrence		
Lymphatic	5	23
Hematogenous	6	23

Locoregional	3	30
Peritoneal	2	12
Second recurrence	5	3
OS, mean ± SD (months)		
All patients	44.80 ± 34.65	20.6 ± 27.58
Censored patients (follow-up time)	124.00 ± 50.82	64.41 ± 44.58
Deceased patients (OS)	77.60 ± 61.39	47.73 ± 58.19

*All values for histological components are cumulative and based on tumors with multiple documented histologic subtypes. As a result, the reported numbers do not reflect the number of tumors with a specific histology but rather the total number of occurrences of each histological component across all cases. Percentages refer to the respective group sizes.

3.3. Survival Analysis

3.3.1. Impact of Surgery on Overall Survival

FIGO IV

To determine whether surgery impacts survival, a Kaplan-Meier survival analysis was performed, comparing patients with and without surgery within the FIGO stage IV subgroup. Among the eight non-operated patients, four had died and four were censored at last follow-up. Out of the 16 operated patients, six had died and 10 were censored.

<u>Non-operated group:</u>

- Mean survival: 22.43 months (SE = 8.72, CI 95% [5.34, 39.52])
- Median survival: 6.0 months (SE = 5.24, CI 95% [0, 16.27])

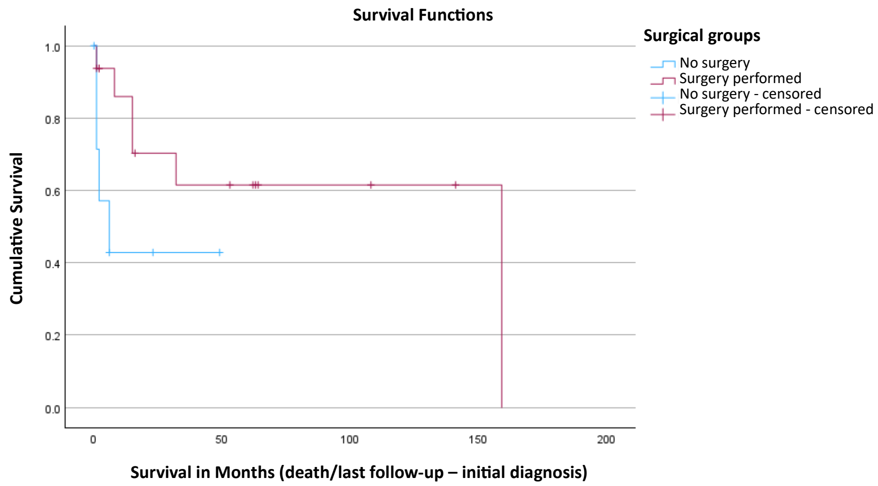
<u>Operated group:</u>

- Mean survival : 103.67 months (SE = 21.55, CI 95% [61.44, 145.90])
- Median survival: 159.0 months (SE = 0, no CI calculated)

The log-rank (Mantel-Cox) test revealed a chi-square of 2.854 with 1 degree of freedom ($p = 0.091$), indicating a trend toward improved survival in the operated group, though this did not reach statistical significance.

The Kaplan-Meier curve (Figure 3) illustrates a visibly prolonged survival in patients who underwent surgery compared to those who did not.

Figure 3: Kaplan-Meier curve of overall survival by surgical groups (FIGO IV cohort)



A univariate Cox proportional-hazards analysis was conducted in 23 women with FIGO stage IV endometrial carcinoma to quantify the effect of cytoreductive surgery on overall survival. In this cohort, 10 patients died (events) and 13 were censored at last follow-up.

The omnibus likelihood ratio test comparing the surgery model to the null model yielded $\chi^2(1) = 2.702$ ($p = 0.100$), indicating that inclusion of surgical status did not reach statistical significance but suggested a trend toward improved discrimination.

The estimated hazard ratio (HR) for surgery was 0.34 (CI 95% [0.08, 1.44]), signifying that, at any given time, patients who underwent cytoreductive surgery faced approximately one-third the risk of death compared with those who did not undergo surgery. The Wald test for this coefficient produced $p = 0.115$, indicating that, in this sample, the observed reduction in hazard could not be distinguished from chance at the 5% significance level.
Although the p-value exceeds 0.05, the hazard ratio of 0.34 suggests a substantial survival benefit associated with surgery. In practical terms, a hazard ratio well below 1.0 indicates that surgery may meaningfully prolong survival in this high-risk population. The most likely explanation for the p-value above 0.05 is the limited number of events (only 10 deaths), which reduces statistical power. To confirm this potential survival advantage, larger cohorts or multivariable analyses that adjust for additional prognostic factors are required.

In summary, univariate Cox analysis in the FIGO IV cohort indicates a pronounced, though not statistically definitive, reduction in mortality risk for patients receiving cytoreductive surgery (HR ≈ 0.34).

Recurrence

Survival following first recurrence was then assessed. In the non-operated cohort (n = 52), 30 patients had died and 22 were censored at last follow-up; in the operated cohort (n = 10), 5 patients had died and 5 were censored.

Non-operated group:

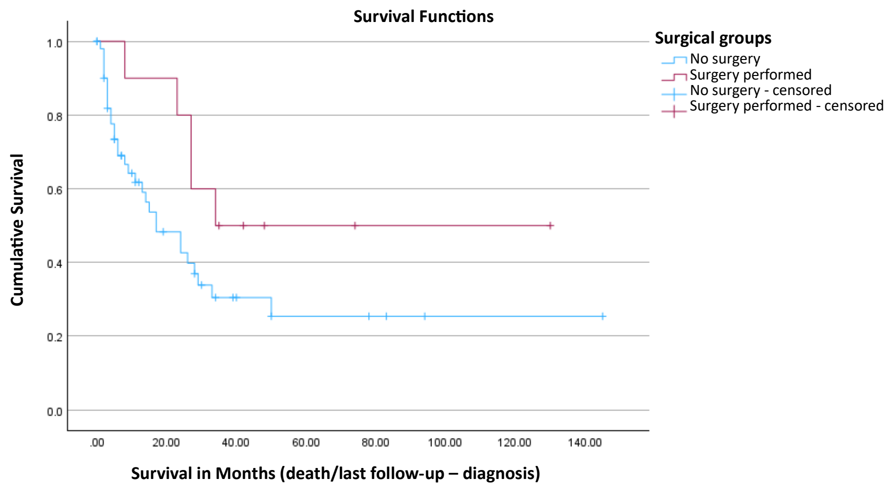
- Mean survival: 48.08 months (SE = 9.82; CI 95% [28.82, 67.33])
- Median survival: 17.0 months (SE = 5.62; CI 95% [5.98, 28.02]).

Operated group:

- Mean survival : 76.90 months (SE = 16.90; CI 95% [43.77, 110.03])
- Median survival: 34.0 months (SE not estimable).

By log-rank (Mantel-Cox) test, the difference in survival curves yielded $\chi^2 = 2.631$ with 1 df ($p = 0.105$), indicating a trend toward improved survival in operated patients that did not reach statistical significance (Figure 4).

Figure 4: Kaplan-Meier curve of overall survival by surgical groups (Recurrence cohort)



Also a univariate Cox proportional-hazards analysis was performed in 60 patients with recurrent endometrial cancer to evaluate the effect of cytoreductive surgery on overall survival. In this group, 35 patients died (events), while 25 were censored at last follow-up. Two additional cases were excluded due to implausible censoring times, resulting in 60 evaluable patients.

The omnibus likelihood ratio test comparing the surgery model to the null model yielded $\chi^2(1) = 1.128$ ($p = 0.288$), indicating that the inclusion of surgical status did not significantly improve the model's ability to discriminate between longer-term survivors and non-survivors in this cohort.

The estimated hazard ratio (HR) for surgery was 21.55 (SE = 4.380), with a non-significant Wald test p-value of 0.483. At face value, this suggests that, at any given time, patients who underwent surgery had a substantially higher risk of death than those who did not. However, this unexpected result is highly uncertain and should be interpreted with caution. Given the limited number of surgically treated patients (n = 10) compared to the overall number of events, the large standard error and the unstable estimate indicate a high degree of imprecision.

Although the point estimate indicates a markedly elevated hazard, the result is not statistically significant and likely reflects model instability rather than a true association. The limited number of operated patients in this cohort restricts the reliability of the coefficient and contributes to wide confidence intervals (not reported by SPSS due to estimation issues).

In summary, univariate Cox analysis in the recurrent-disease cohort did not show a statistically reliable effect of surgery on overall survival. The extreme hazard ratio and lack of statistical significance underscore the limitations of this small subgroup and highlight the need for further analysis in larger samples or in multivariable models adjusting for other clinical prognostic factors.

3.3.2. Extent of Surgical Influence on Survival

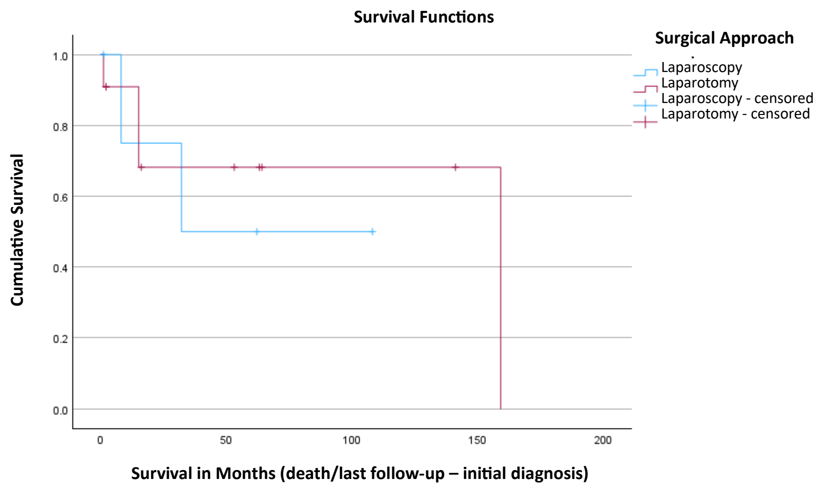
FIGO IV

Within the 16 patients with FIGO stage IV disease who underwent cytoreductive surgery, the influence of individual clinical and treatment factors on overall survival next examined next. During follow-up, six patients were found to have died, and ten were censored.

<u>Surgical Approach</u>

Median survival was longer following laparotomy (Mdn = 159 months; M = 111.9 ± 26.2 months) compared with laparoscopic surgery (Mdn = 32 months; M = 64.0 ± 22.4 months), but this difference did not reach significance (log-rank $\chi^2(1) = 0.18$; $p = 0.669$). The wide confidence intervals reflect the limited numbers in each group (n = 11 open, n = 5 laparoscopy).

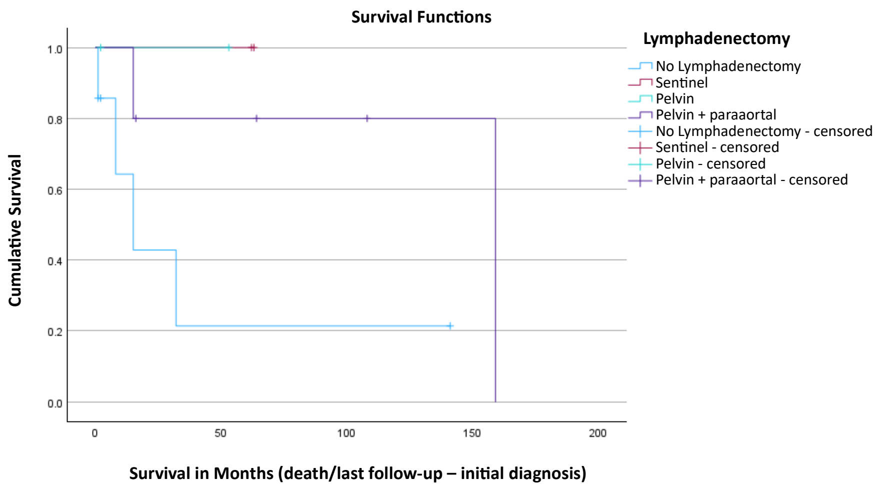
Figure 5: Kaplan-Meier curve of overall survival by surgical approach (FIGO IV cohort)



<u>Lymphadenectomy Extent</u>

Patients undergoing combined pelvic + para-aortic lymphadenectomy (n = 5) tended to have longer survival than those with no or limited nodal dissection, but the overall comparison was not significant (log-rank $\chi^2(3) = 6.06$; $p = 0.109$).

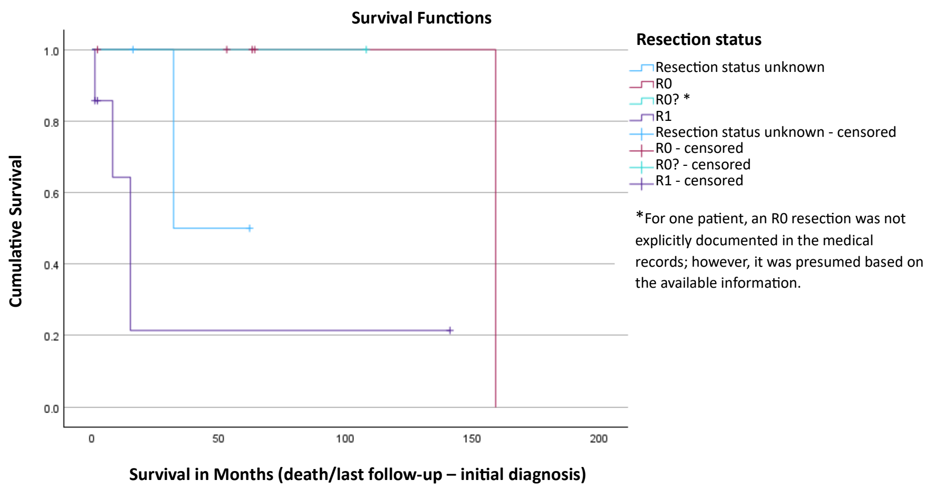
Figure 6: Kaplan-Meier curve of overall survival by lymphadenectomy (FIGO IV cohort)



<u>Resection Status</u>

Completeness of tumor removal was the factor closest to significance: patients with R0 resection (n = 6) experienced one death, whereas those with R1 resection (n = 7) had four deaths (log-rank $\chi^2(3) = 7.59$; $p = 0.055$). This suggests a meaningful survival advantage for complete cytoreduction, narrowly missing the $p < 0.05$ threshold.

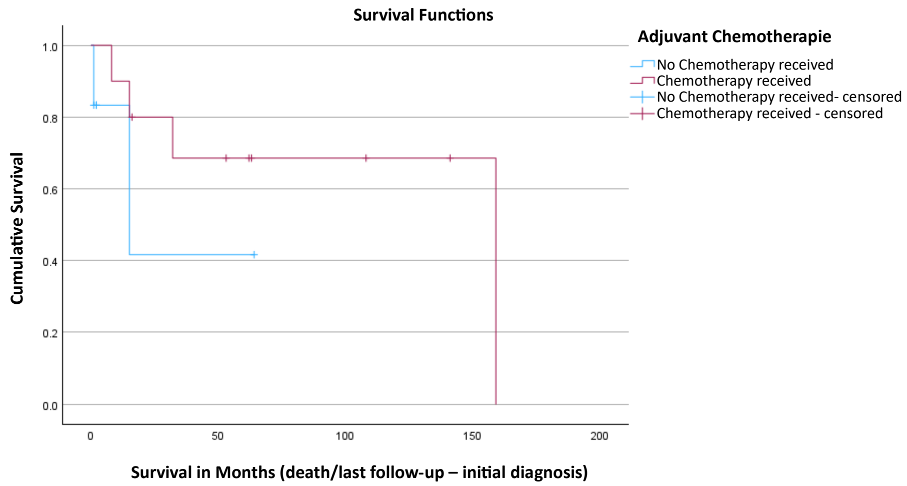
Figure 7: Kaplan-Meier curve of overall survival by resection status (FIGO IV cohort)



<u>Adjuvant Chemotherapy</u>

Those receiving postoperative chemotherapy (n = 10) showed a higher mean survival (114.99 ± 24.46 months; Mdn = 159 months) than those managed without chemotherapy (33.08 ± 15.58 months; Mdn = 15 months). The log-rank test yielded $\chi^2(1) = 1.25$ ($p = 0.263$), indicating a strong numeric trend that did not reach statistical significance.

Figure 8: Kaplan-Meier curve of overall survival by adjuvant chemotherapy (FIGO IV cohort)



<u>Antihormonal and Radiation Therapy</u>

Neither adjuvant antihormonal therapy (log-rank $\chi^2(1) = 0.52$; $p = 0.470$) nor radiotherapy (log-rank $\chi^2(1) = 0.10$; $p = 0.752$) produced significant survival differences in this cohort.

Figure 9: Kaplan-Meier curve of overall survival by antihormonal therapy (FIGO IV cohort)

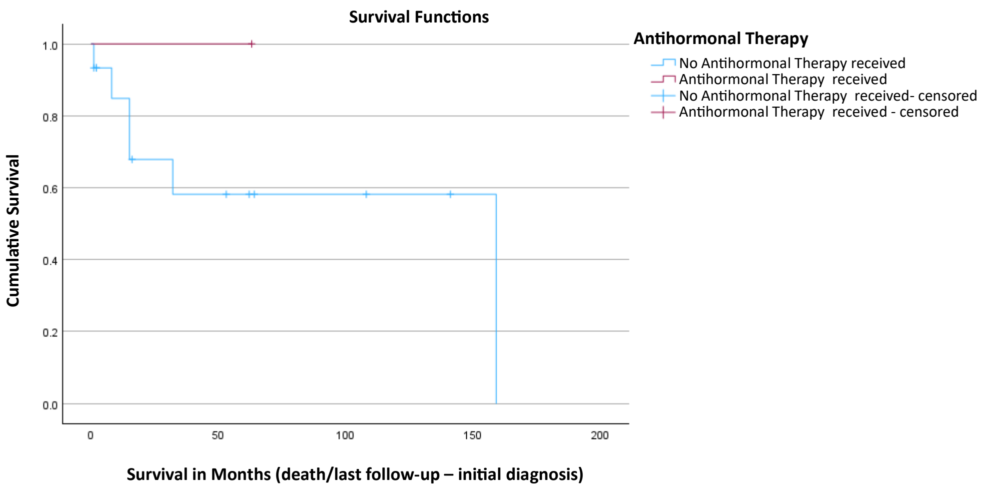
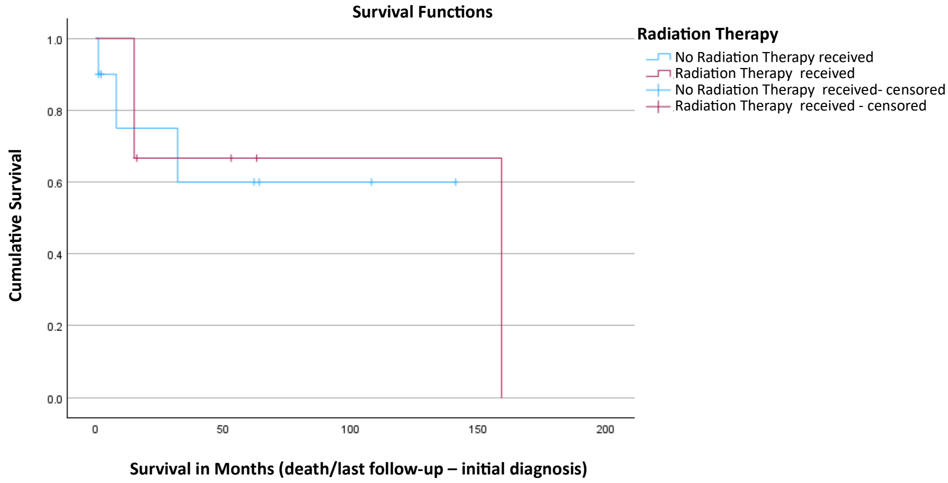


Figure 10: Kaplan-Meier curve of overall survival by radiation therapy (FIGO IV cohort)



Furthermore, univariate Cox proportional hazards models were fitted to evaluate the impact of individual surgical and adjuvant factors on overall survival. In each model, only one covariate was entered to avoid overfitting, given the small number of events (n = 6).

<u>Surgical Approach: Laparoscopy vs. Laparotomy</u>

When comparing laparoscopic versus open abdominal surgery, the estimated hazard ratio was 1.47 (CI 95% [0.24, 8.83]), suggesting a 47% higher risk of death for patients who underwent laparoscopy. However, this difference was not statistically significant (p = 0.677), and the wide confidence interval indicates a high degree of uncertainty. These results imply that, based on the current data, no reliable conclusion can be drawn about which surgical approach offers better survival.

<u>Extent of Lymphadenectomy</u>

The analysis of lymph node dissection strategies (none vs. sentinel node vs. pelvic vs. combined pelvic + paraaortic) did not show a significant association with overall survival (overall p = 0.120). Specifically, patients with combined pelvic and paraaortic dissection had a hazard ratio of 5.36 compared to those with no dissection, indicating a numerically higher risk of death. However, the 95% confidence interval was extremely wide [0.59, 48.61], and the result was not statistically significant (p = 0.136). The very large confidence intervals and unstable estimates in other group comparisons (e.g., sentinel vs. combined dissection) reflect sparse data, which limits the ability to draw robust conclusions regarding the effect of lymphadenectomy on survival.

Resection Status (R0 vs. R1)

This analysis aimed to determine whether achieving complete tumor resection (R0) was associated with improved survival. The model showed a trend toward significance (overall p = 0.063), but the direct comparison between R0 and R1 yielded an extremely unstable estimate (HR ≈ 0, p = 0.962) with a very large standard error. These values indicate that the data were insufficient to generate a reliable result. Nonetheless, the numerical trend suggests a potential survival benefit with complete resection, aligning with existing literature, though confirmation requires larger patient numbers.

Adjuvant Chemotherapy

Patients who didn't receive adjuvant chemotherapy had a hazard ratio of 2.71 compared to those who did (CI 95% [0.43, 17.05]). This suggests a possible increase in mortality risk, but the difference was not statistically significant (p = 0.289), and the wide confidence interval implies high uncertainty. These findings do not provide clear evidence for or against the benefit of chemotherapy in this cohort.

Adjuvant Antihormonal Therapy

Only one patient received antihormonal therapy, making any comparison extremely unstable. The analysis yielded a hazard ratio of 23.39 (CI 95% [0.00, 1.64×10^7]) for patients **without** antihormonal therapy relative to the single treated patient. A p-value of 0.646 confirms that this estimate is not statistically significant. The enormous confidence interval reflects essentially no reliable information about the effect of antihormonal treatment in this setting.

Adjuvant Radiotherapy

When comparing patients without versus with adjuvant radiotherapy, the hazard ratio was 1.33 (CI 95% [0.22, 8.13]), suggesting a 33% higher risk of death in those not irradiated. Yet, this difference did not reach statistical significance (p = 0.758), and the wide interval again signals that the true effect could range from substantial benefit to considerable harm. Thus, no firm conclusion can be drawn regarding postoperative radiotherapy.

Table 7: Univariate Cox Proportional Hazards Results (FIGO IV Cohort, n = 16)

Variable	Comparison	HR (Exp(B))	CI 95% for HR	p-value
Surgical Approach	Laparoscopy vs. Laparotomy	1.47	[0.24, 8.83]	0.677
Lymphadenectomy	None vs. Pelvic + Paraaortic	5.36	[0.59, 48.61]	0.136
Resection Status	R0 vs. R1	≈ 0.00	[0.00, 1.23×10^{227}]	0.962
Adjuvant Chemotherapy	No vs. Yes	2.71	[0.43, 17.05]	0.289
Adjuvant Antihormonal Therapy	No vs. Yes	23.39	[0.00, 1.64×10^{7}]	0.646
Adjuvant Radiotherapy	No vs. Yes	1.33	[0.22, 8.13]	0.758

<ins>Summary</ins>

Among FIGO IV patients who underwent cytoreductive surgery, neither Kaplan-Meier survival analyses nor univariate Cox regression identified statistically significant associations between clinical or treatment-related factors and overall survival. Completeness of tumor resection (R0 vs. R1) was the only variable to approach significance in both methods (Kaplan-Meier: p = 0.055; Cox regression: p = 0.063), suggesting a potential survival benefit of complete cytoreduction, although hazard estimates were unstable and marked by wide confidence intervals. Other factors - surgical approach (laparoscopic vs. open), extent of lymphadenectomy, and receipt of adjuvant chemotherapy, radiotherapy, or antihormonal therapy - showed numerical trends (e.g. favoring open surgery and postoperative chemotherapy) but remained statistically inconclusive, reflecting the limited number of events and subgroup sizes.

These findings underscore the restricted statistical power of this cohort and the need for larger, more adequately powered studies to determine which surgical and adjuvant strategies truly impact survival in FIGO IV endometrial cancer.

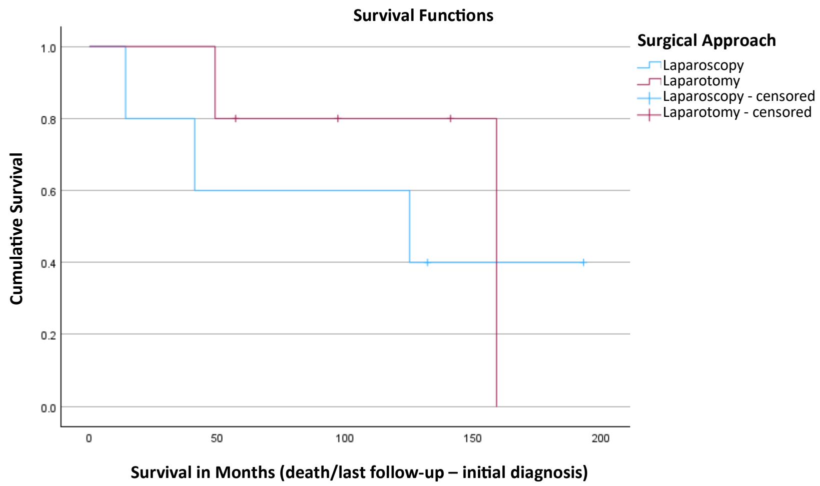
Recurrence

Within the 10 patients who underwent secondary cytoreductive surgery for recurrent endometrial carcinoma, the impact of individual clinical and treatment factors on overall survival was next examined. Over the follow-up period, five patients died and five were censored.

Surgical Approach

Median survival was slightly longer after open abdominal surgery (Mdn = 159 months; M = 137.0 ± 27.8 months) compared with other procedures performed for metastasis removal (such as pulmonary lobectomy or excision of vaginal metastases; Mdn = 125 months; M = 113.2 ± 33.4 months), but this difference did not achieve statistical significance (log-rank $\chi^2(1) = 0.28$; $p = 0.599$). The overlapping confidence intervals reflect the small subgroup sizes (n = 5 open, n = 5 other).

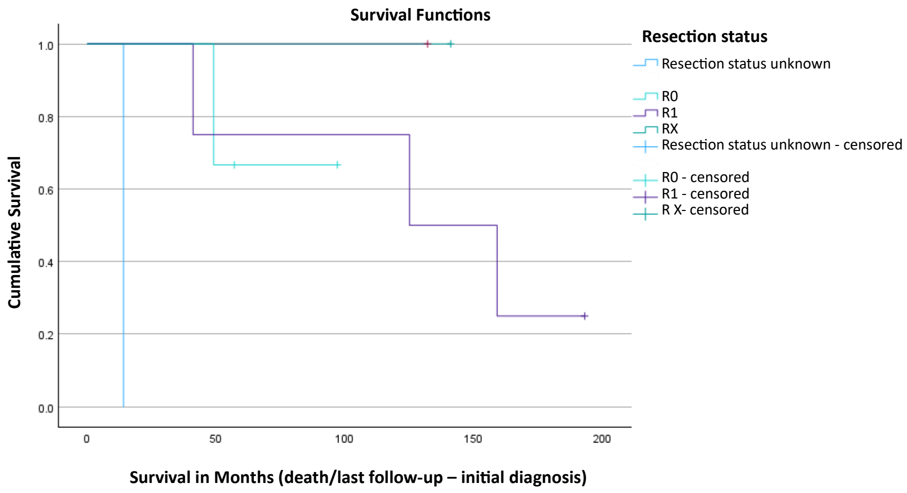
Figure 11: Kaplan-Meier curve of overall survival by surgical approach (Recurrence cohort)



Resection Status

When stratified by completeness of resection, patients with R0 resection (n = 3) experienced one death and two censorings, whereas those with R1 resection (n = 4) had three deaths and one censoring; one case was unknown. The overall comparison was significant (log-rank $\chi^2(4) = 10.01$; $p = 0.040$), indicating that complete tumor removal at recurrence confers a meaningful survival advantage.

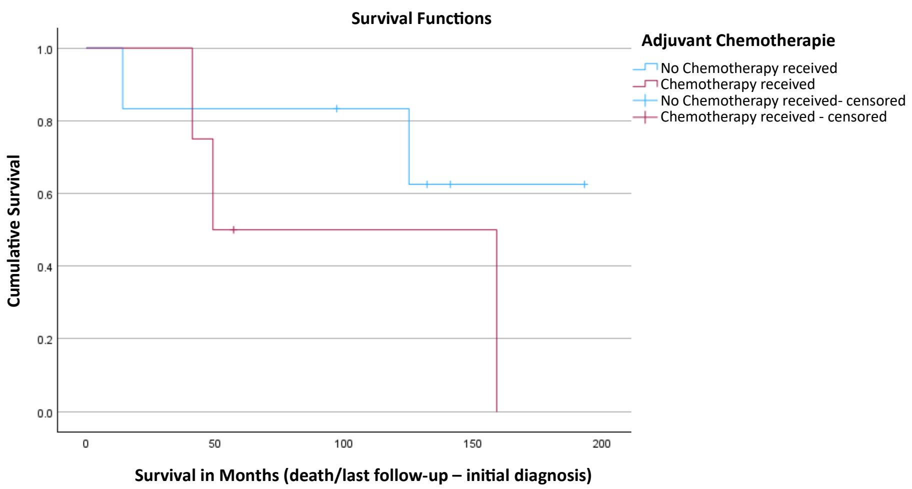
Figure 12: Kaplan-Meier curve of overall survival by resection status (Recurrence cohort)



Adjuvant Chemotherapy

Patients who did not receive chemotherapy after recurrence showed a numerically longer mean survival (149.0 ± 27.5 months; median not estimable) than those who did (102.0 ± 34.9 months; Mdn = 49.0 months), yet this difference was not statistically significant (log-rank $\chi^2(1) = 1.03$; $p = 0.310$). Wide intervals again indicate considerable uncertainty in these estimates.

Figure 13: Kaplan-Meier curve of overall survival by adjuvant chemotherapy (Recurrence cohort)

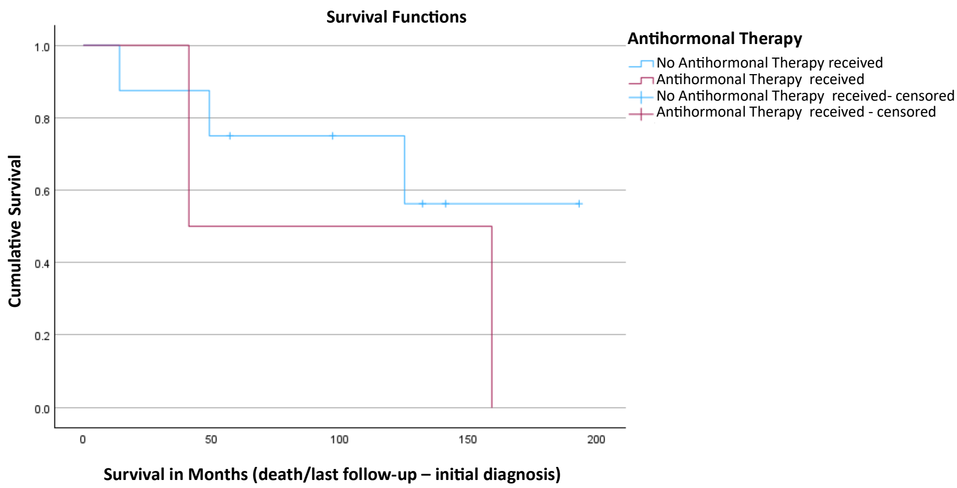


Antihormonal Therapy

Comparison by antihormonal therapy revealed mean survival of 139.9 ± 24.9 months (median not estimable) in the no-therapy group (n = 8) versus 100.0 ± 59.0 months (Mdn =

41.0 months) in the treated group (n = 2). This difference failed to reach significance (log-rank $\chi^2(1) = 0.67$; $p = 0.415$), reflecting both the very small treated subgroup and imprecise estimates.

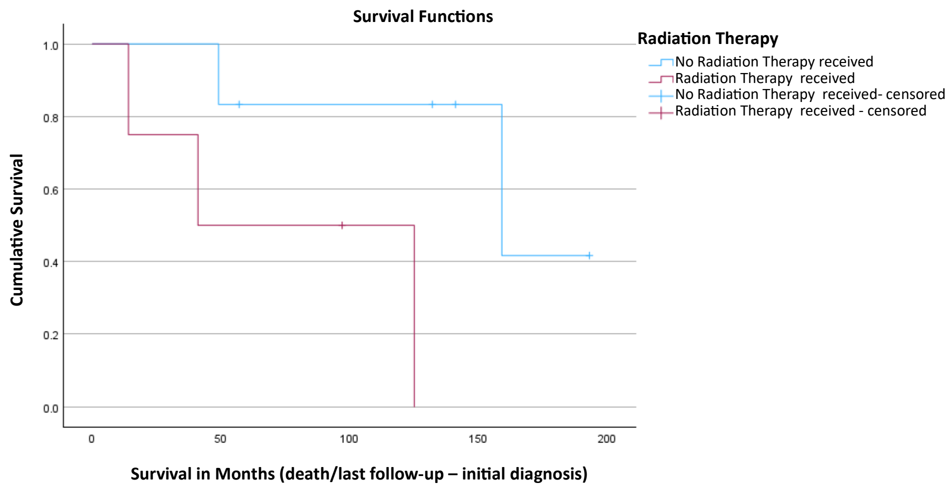
Figure 14: Kaplan-Meier curve of overall survival by antihormonal therapy (Recurrence cohort)



<u>Radiotherapy</u>

Patients who did not receive radiotherapy after recurrence (n = 7) had a mean survival of 154.8 ± 21.8 months (Mdn = 159.0 months), whereas those who did (n = 3) had a mean survival of 76.3 ± 30.4 months (Mdn = 41.0 months). This difference was statistically significant (log-rank $\chi^2(1) = 4.08$; $p = 0.044$), suggesting that, in this small cohort, radiotherapy at recurrence was associated with shorter survival, though this counterintuitive finding may reflect selection bias (sicker patients being offered radiation) and requires confirmation in larger samples.

Figure 15: Kaplan-Meier curve of overall survival by radiation therapy (Recurrence cohort)



Moreover, a univariate Cox proportional hazards analysis was conducted to evaluate the impact of individual treatment and surgical factors on overall survival in the recurrent-disease cohort. In each model, only one covariate was entered to avoid overfitting, given the limited number of events (n = 5).

<u>Surgical Approach</u>

When comparing non-abdominal metastasis removal procedures (e.g. pulmonary lobectomy, vaginal excision) to open laparotomy, the hazard ratio was 1.62 (CI 95% [0.27, 9.86]; p = 0.603). This point estimate suggests a 62% higher risk of death for patients undergoing alternate metastasis resections, but the wide confidence interval and non-significant p-value indicate a high degree of uncertainty and preclude definitive conclusions about which surgical approach is preferable.

<u>Extent of Metastasis Resection</u>

Completeness of resection during surgery at recurrence was significantly associated with survival (overall p = 0.040). When using RX (unknown resection status) as the reference, both R0 and R1 resections produced extremely large hazard ratios (HR = 208-241) with highly unstable estimates and extremely wide confidence intervals. These values are not statistically significant on their own but suggest that the model was sensitive to small sample fluctuations. Nonetheless, the overall model's significance supports the assumption that resection status may meaningfully influence survival (consistent with existing literature).

Adjuvant Chemotherapy

Patients who did not receive chemotherapy after recurrence had a hazard ratio of 0.40 (CI 95% [0.06, 2.50]) compared to those who did receive it, suggesting a 60% lower mortality risk. This difference, however, was not statistically significant (p = 0.324) and may be influenced by confounding factors, such as selection bias. The wide confidence interval and modest number of events indicate that these findings should be interpreted with caution.

Adjuvant Antihormonal Therapy

When comparing patients who received antihormonal therapy after recurrence with those who did not, the hazard ratio was 0.46 (CI 95% [0.07, 3.04]), indicating a 54 % reduction in the estimated risk of death in the no-therapy group. However, this difference was also not statistically significant (p = 0.423), and the wide confidence interval again reflects uncertainty. These results do not provide reliable evidence regarding the efficacy of antihormonal therapy in this cohort.

Adjuvant Radiotherapy

In contrast to the other treatment modalities, absence of radiotherapy after recurrence showed a statistically significant association with improved survival. Patients who did not receive radiotherapy had a hazard ratio of 0.13 (CI 95% [0.01, 1.30]) compared to those who did, corresponding to an 87% reduction in the estimated risk of death. While this difference approached significance (p = 0.083), the overall model yielded a chi-square of 4.08 (p = 0.044), indicating a significant difference in survival curves. Nevertheless, this counterintuitive finding may reflect confounding by indication (i.e., patients with worse prognoses may have been more likely to receive radiation) and should be interpreted with caution.

Table 8: Univariate Cox Proportional Hazards Results (Recurrent Disease Cohort, n = 10)

Variable	Comparison	HR	CI 95%	p-value
Surgical Approach	Non-abdominal vs. Laparotomy	1.62	[0.27, 9.86]	0.603
Metastasis Resection Status	R0 vs. RX*	241.21	[0.00, 1.09×10^18]	0.765
	R1 vs. RX	208.90	[0.00, 8.90×10^17]	0.771
Adjuvant Chemotherapy	No vs. Yes	0.40	[0.06, 2.50]	0.324

Adjuvant Antihormonal Therapy	No vs. Yes	0.46	[0.07, 3.04]	0.423
Adjuvant Radiotherapy	No vs. Yes	0.13	[0.01, 1.30]	0.083

*"RX" denotes unknown resection status, used as the reference category.

Summary

In the group of patients treated with secondary cytoreduction for recurrent endometrial carcinoma, neither Kaplan-Meier analysis nor univariate Cox models identified the surgical method, adjuvant chemotherapy, or antihormonal therapy as significant predictors of overall survival. Although those who underwent open laparotomy had a higher median survival (159 months) compared to other metastasectomy procedures (125 months), this difference was not statistically significant (log-rank p = 0.599; Cox HR 1.62, CI 95% [0.27, 9.86]; p = 0.603). Likewise, patients who did not receive postoperative chemotherapy or antihormonal treatment showed somewhat better survival estimates, but neither trend reached significance (KM p = 0.310 and 0.415; Cox p = 0.324 and 0.423), and confidence intervals remained broad.

The only variable to emerge as significant in both analyses was the completeness of tumor removal: achieving an R0 resection conferred a marked survival benefit (KM p = 0.040; overall Cox model p = 0.040), even though individual hazard ratios were imprecise. In contrast, those who received radiotherapy at recurrence experienced worse outcomes (KM p = 0.044), and although the Cox model suggested a high hazard ratio (~7.7, CI 95% [0.47, 128.1]), this did not reach, but approached, statistical significance (p = 0.083), likely attributable to the selection of higher-risk patients for radiation, causing a selection-bias. These findings underscore the paramount importance of complete cytoreduction at relapse while also highlighting the limited power of this small series and the need for validation in larger, prospective cohorts.

3.3.3. Preoperative Predictors of Surgical Benefit

FIGO IV

Univariate Cox proportional-hazards models were fitted, one per covariate, to explore which factors present before surgery might predict overall survival among the 16 patients with FIGO IV disease who underwent cytoreductive surgery (6 deaths, 10 censored).

Age at Diagnosis

The hazard ratio (HR) for each additional year of age was 1.03 (CI 95% [0.94, 1.13]; p = 0.499), indicating essentially no change in mortality risk with increasing age. The log-rank comparison yielded $\chi^2(1) = 0.47$, p = 0.495, confirming the lack of association between patient age and survival in this small cohort.

Body Mass Index (BMI)

BMI emerged as the only statistically significant preoperative predictor. Each one-unit increase in BMI was associated with a 25% higher hazard of death (HR = 1.25; CI 95% [1.01, 1.54]; p = 0.039). The model's chi-square was 5.07 (df = 1), p = 0.024, suggesting that higher BMI may be linked to poorer outcomes after cytoreductive surgery in FIGO IV patients, although the wide confidence interval indicates moderate imprecision.

FIGO Substage

Comparisons across substages (IV vs. IVb as reference vs. IVa) did not reveal any significant survival differences (overall $\chi^2(2) = 1.51$; p = 0.471). For example, patients with plain "IV" disease had an HR of 1.89 versus IVb (CI 95% [0.31, 11.73]; p = 0.494). These results imply that, within this surgically treated group, finer distinctions of substage do not meaningfully stratify prognosis.

Tumor Grade

No association was observed between histologic grade and survival (overall $\chi^2(3) = 0.76$; p = 0.859). Hazard estimates for Grade 2 and Grade 3 tumors relative to Grade 3/4 were highly unstable (HRs >10, extremely wide CIs), reflecting insufficient events per category.

Histological Subtype

When comparing endometrioid, serous, clear cell, carcinosarcoma, and other subtypes against the rare undifferentiated reference, the overall model was significant ($\chi^2(7) = 21.92$; p = 0.003), but none of the individual subtype contrasts yielded interpretable hazard ratios (all were effectively 1.0 with infinite confidence intervals). This finding likely stems from sparse observations in most histologic categories.

Endometrial Type (I vs. II)

No survival difference was detected between Type I and Type II carcinomas (overall $\chi^2(3) = 1.31$; $p = 0.727$). The HR for Type I versus Type II was 0.41 (CI 95% [0.04, 3.94]; $p = 0.439$), again underscoring limited power.

Presence of Metastases at Diagnosis

Patients without metastases at diagnosis showed a numerically lower hazard (HR = 0.04; CI 95% [0.00, 1,379.99]; $p = 0.542$) compared to those with metastases, but this difference was not statistically significant ($\chi^2(1) = 0.93$; $p = 0.335$) and the estimate is highly imprecise.

Summary

Among the preoperative factors evaluated, only **BMI** showed a statistically significant association with overall survival in this FIGO IV surgical cohort, suggesting that higher BMI may confer increased risk of death following cytoreductive surgery. All other variables (age, substage, grade, histologic subtype, endometrial type, and metastatic status) yielded non-significant hazard ratios with wide confidence intervals, reflecting the very small sample size and limited number of events.

Table 9: Univariate Preoperative Predictors of Overall Survival (FIGO IV Surgery Cohort)

Variable	Comparison	HR (Exp(B))	CI 95%	p-value
Age at Diagnosis	per 1-year increase	1.03	[0.94, 1.13]	0.499
BMI	per 1 kg/m² increase	1.25	[1.01, 1.54]	0.039
FIGO Substage	IV vs. IVb (reference)	1.89	[0.31, 11.73]	0.494
	IVa vs. IVb (reference)	~0.00*	[0.00, ∞]	0.987
Tumor Grade	G2 vs. G3/4 (reference)	-†	-	-
	G3 vs. G3/4 (reference)	-†	-	-
Histologic Subtype	-	-†	-	-

Endometrial Type	Type I vs. Type II (reference)	0.41	[0.04, 3.94]	0.439
Metastases at Diagnosis	No vs. Yes (reference)	0.04*	[0.00, 1,379.99]	0.542

* Estimates are highly unstable due to sparse data or zero events in comparator groups.

† Individual grade comparisons yielded extremely large standard errors and confidence intervals; omitted for clarity.

‡ Overall likelihood-ratio test across all histologic subtypes was significant, but individual hazard ratios were not interpretable.

Recurrence

To identify patient-related characteristics predictive of survival benefit from surgery in recurrent endometrial cancer, univariate Cox proportional hazards models were applied to the operated subgroup (n = 10). Each model included only one covariate to avoid overfitting, given the limited number of events (n = 5).

<u>Age at Diagnosis</u>

Age at the time of recurrence surgery was not significantly associated with overall survival. The hazard ratio was 0.975 per year (CI 95% [0.898, 1.058]; p = 0.545), suggesting that older or younger age did not meaningfully influence the prognosis in this small cohort.

<u>Body Mass Index (BMI) at Initial Diagnosis</u>

An inverse relationship between BMI and mortality was observed, with higher BMI associated with lower estimated risk of death (HR: 0.655; CI 95% [0.329, 1.303]). However, this result did not reach statistical significance (p = 0.228). While the trend suggests a potential protective effect of higher BMI, the wide confidence interval reflects high uncertainty.

<u>FIGO Substage at Initial Diagnosis</u>

Survival outcomes varied across FIGO substages, with the overall model approaching statistical significance (p = 0.062). However, individual comparisons, such as stage Ia versus IVb or IIIc1 versus IVb, produced extremely wide confidence intervals and unstable hazard estimates. For instance, patients with FIGO Ib disease had an HR of 71,693,226 (CI 95% [0.000, 8.79×10^{263}]; p = 0.952), underscoring the limitations of the dataset and the resulting imprecision of estimates.

Tumor Grading

No significant differences in survival were found between patients with G1, G2, or G3 tumors (overall p = 0.206). Although the HR for G1 versus G3 was estimated as 0 (HR = 0.000; CI 95% [0.000, 2.998×10^{287}]), the extremely wide confidence interval and large standard error indicate that the estimate is statistically unreliable due to very low numbers in the subgroups.

Histologic Subtype

The overall comparison across histologic subtypes (endometrioid, serous, clear cell, mixed) showed statistical significance (p = 0.008). However, specific contrasts, such as endometrioid vs. serous/clear cell, did not reach significance (HR = 0.086; CI 95% [0.004, 1.792]; p = 0.113), but may suggest a potential trend toward better outcomes in patients with endometrioid histology. These results must be interpreted cautiously due to instability in the estimates and the small group sizes.

Endometrial Type

When comparing type I and type II tumors, patients with type I histology had a lower estimated hazard of death (HR = 0.086; CI 95% [0.004, 1.792]), but this finding did not reach statistical significance (p = 0.113). While suggestive of a prognostic difference, the wide interval and p-value reflect limited statistical power.

Initial Treatment Characteristics

Several variables related to the initial treatment at the time of first diagnosis (prior to recurrence) were also evaluated. The type of primary surgery (laparotomy vs. laparoscopy), extent of resection, lymphadenectomy, and receipt of adjuvant chemotherapy or radiotherapy were included in the analysis:

- Initial Surgical Approach showed a non-significant trend toward better survival in patients who had undergone laparotomy compared to laparoscopy (HR = 0.35; CI 95 % [0.10, 1.21]; p = 0.098).

- Extent of Initial Lymphadenectomy was not significantly associated with survival (overall p = 0.013), also individual comparisons produced highly unstable hazard ratios, such as for sentinel dissection (HR = 454,186.49; p = 0.968), indicating statistical unreliability.
- Initial resection status, chemotherapy, and radiotherapy also did not show significant associations with survival, with all hazard ratios either close to 1.0 or exhibiting excessive uncertainty.

Presence of Metastases at Recurrence

Neither the presence nor specific distribution of metastatic sites at the time of recurrence appeared to influence survival in a statistically meaningful way. Models examining lymphogenic, locoregional, hematogenous, and cavitary metastases all returned non-significant results with extremely unstable estimates. For example, the presence of pelvic lymph node metastases versus mediastinal nodes yielded a hazard ratio of 1.19 (CI 95% [0.06, 22.33]; p = 0.906), with similar findings across other comparisons.

Table 10: Univariate Preoperative Predictors of Overall Survival (Recurrent Disease Surgery Cohort)

Variable	Comparison	HR (Exp(B))	CI 95%	p-value
Age at diagnosis (years)	per 1-year increase	0.98	[0.90, 1.06]	0.545
BMI (kg/m²)	per 1-unit increase	0.66	[0.33, 1.30]	0.228
FIGO substage	Ia vs IVb	1.56×10^2	[0.00, 1.84×10^13]	0.698
	Ib vs IVb	7.17×10^7	[0.00, 8.79×10^263]	0.952
	IIIc1 vs IVb	1.69×10^2	[0.00, 2.05×10^13]	0.694
Tumor grading	G1 vs G3	0.00	[0.00, 2.99×10^287]	0.970
	G2 vs G3	0.82	[0.08, 8.02]	0.866
Histologic subtype	Endometrioid vs Serous + Clear cell	0.09	[0.004, 1.79]	0.113

Endometrial type	Type I vs Type II	0.09	[0.004, 1.79]	0.113
Presence of metastases at recurrence	No vs Yes	0.04	[0.00, 1,379.99]	0.542
Initial surgical approach	Laparoscopy vs Laparotomy	0.35	[0.10, 1.21]	0.098
Extent of initial lymphadenectomy	None vs Pelvic + Paraaortic	0.24	[0.03, 2.37]	0.224
Initial chemotherapy	No vs Yes	0.92	[0.15, 5.63]	0.932
Initial radiotherapy	No vs Yes	0.32	[0.05, 1.98]	0.219

Note: All confidence intervals are extremely wide, and many hazard estimates are unstable. These results are exploratory and highlight the need for larger cohorts to obtain reliable prognostic estimates.

Summary

In this recurrence surgery cohort, none of the analyzed preoperative or initial treatment variables were clearly associated with overall survival in univariate Cox regression. While some trends, such as better outcomes in patients with endometrioid histology or type I tumors, were observed, these did not reach statistical significance and were accompanied by wide confidence intervals. The small sample size and low number of events greatly limit the interpretability and robustness of the findings. As such, these analyses should be regarded as exploratory, and larger datasets are needed to confirm potential prognostic indicators in patients undergoing salvage surgery for recurrent endometrial cancer.

4. Discussion

The results of this study confirm the important role of cytoreductive surgery in the management of both advanced (FIGO IV) and recurrent endometrial cancer. Consistent with prior literature, surgical treatment was associated with numerically improved survival outcomes, particularly when complete macroscopic tumor resection (R0) could be achieved. Although the retrospective design and limited sample size precluded statistical significance in some subgroup analyses, the observed trends align with previous studies that highlight cytoreduction as a key prognostic factor.

In 1994, Goff et al. showed in their analysis of 47 cases of stage IV disease that those 29 women with surgically resectable tumors had a median survival of 18 months, compared to only 8 months in those who did not receive surgical treatment ($p = 0.0001$). (27) Chi et al. (1997) were the first to rigorously investigate the role of surgical cytoreduction in stage IV endometrial cancer and found that there was no statistically significant difference in survival between patients with metastases measuring 2 cm or less before surgery and those who initially had metastases greater than 2 cm but were optimally cytoreduced. (28) This indicates that, even in cases of advanced disease, aggressive surgical tumor reduction may improve survival outcomes. (28) This was also demonstrated in a more recent study by Kanno et al. (2023), which investigated the impact of intra-abdominal cytoreductive surgery in the treatment of endometrial cancer with distant metastasis (stage IVb). In patients who underwent cytoreductive surgery overall survival (OS) was 17 months, compared to 7 months for patients who received only chemotherapy, despite the high residual rate of distant metastases after intra-abdominal cytoreductive surgery. (29)

In 2006, Bristow et al. were the first to compare surgically and non-surgically treated patients with recurrent endometrial cancer. In their study of 61 patients with recurrent endometrial cancer, 35 patients underwent surgery and had a median survival of 28 months, notably longer than the 13 months observed in the nonsurgical group ($p < 0.0001$). (30) Furthermore, Moukarzel et al. (2001) showed that patients undergoing cytoreductive surgery for recurrent endometrial cancer achieved notably better outcomes than those receiving non-surgical therapy. The surgical group showed a median progression-free survival (PFS) of 14.9 months and overall survival (OS) of 57.6 months, resulting in an 80.9% 2-year OS rate. In comparison, the non-surgical group had a median PFS of 8.6 months and an OS of 24.5 months, with both differences being statistically significant ($p < 0.001$). (31) Shikama et al. (2019) found median overall survival to be significantly better for patients receiving surgical

treatment (45months) compared to patients treated with chemotherapy (16 months) or radiotherapy (26 months). (32)
Just as in advanced-stage endometrial carcinoma, achieving optimal cytoreduction also plays a crucial role in cases of recurrence. Achieving complete cytoreduction was identified as a significant independent factor linked to better overall and progression-free survival outcomes.

Another key result of our analysis, despite wide confidence intervals, was the association between R0 resection and improved survival, which emphasizes the clinical value of achieving complete cytoreduction.
In the small FIGO IV cohort, a complete (R0) resection yielded a strong trend toward longer survival, despite the limited sample size. This trend is consistent with observations by Ayhan et al., who reported 25 vs. 10 months median survival for optimally vs. suboptimally debulked patients ($p = 0.001$). Ayhan et al. (2002) were also able to demonstrate a survival advantage for maximal cytoreduction, reporting a median survival of 48 months if left with only microscopic disease compared with 13 months in patients with optimal but macroscopic residual disease. (33)
More recent analyses confirm that pattern; for example, Kanno et al. (2023) found that patients with no macroscopic residual achieved median overall survival of 44 months versus only 9 months for those with residual disease. (29) In a retrospective analysis, Bristow et al. (2000) found that the median survival was 34 months for patients who underwent optimal cytoreductive surgery (defined as residual disease of 1 cm or less), compared to 11 months for those with residual disease larger than 1 cm. In patients who underwent optimal cytoreduction, those with microscopic residual disease experienced a significantly longer median survival than those with optimal but macroscopic residual disease (41 vs. 15 months; $p = 0.0001$), which highlights the importance of striving for maximal cytoreduction. (34)
In this context, our trend toward improved survival with complete resection in FIGO IV patients, though not reaching strict statistical significance, carries clear clinical relevance. The failure to reach $p < 0.05$ likely reflects limited power in our cohort of 16 patients, but the direction and consistency with the literature suggest a true survival advantage for maximal debulking.
In the recurrent endometrial cancer cohort, complete cytoreduction was the only significant predictor of survival. Patients who achieved R0 resection had markedly longer post-

recurrence survival (Mdn = 39.0 months) than those left with any gross tumor (Mdn = 13.5 months, p = 0.0005). The hazard estimates for resection completeness in our Cox model were unstable (large confidence intervals) due to the small surgically treated subgroup, but the association was statistically significant (p = 0.040). This finding aligns closely with multiple reports that surgical excision of recurrent disease prolongs survival. Bristow et al. (2006) reported that recurrent endometrial cancer patients undergoing complete secondary cytoreduction had a median survival of 39.0 months versus 14 months with residual disease (p = 0.0005). (30) Likewise, Scarabelli (1998) and Campagnutta (2004) found that recurrent patients with no macroscopic residual had significantly better progression-free and overall survival compared to those with residual tumor. (35, 36) More recent work by Shikama et al. (2019) also demonstrated a dramatic difference: median survival was 68.0 months after complete secondary cytoreduction versus 20.0 months with residual disease (p = 0.001) (32). Given this consistent evidence, the statistically significant benefit of R0 resection in our recurrent cohort reinforces the clinical imperative to achieve maximal debulking when feasible. Even though our hazard ratios were imprecise, the concordance of multiple studies on this point lends confidence that the association is valid rather than a statistical anomaly.

Other factors in the FIGO IV group (extent of lymphadenectomy, use of adjuvant chemotherapy or radiation, and laparoscopic versus open approach) showed no significant survival differences. This is not surprising given small numbers and heterogeneous treatments. In the literature, benefits of adjuvant therapies in stage IV disease have been variably reported. For instance, Barlin's meta-analysis (2010) found that a higher proportion of patients receiving radiation correlated with longer median survival (2), whereas our data showed no clear effect of postoperative radiotherapy or chemotherapy, likely a reflection of selection bias (patients with worse disease might receive more aggressive therapy). In our recurrent-disease cohort, we did observe an association between *absence* of radiotherapy and better survival, a counterintuitive finding that is most likely confounded by indication. In many retrospective series, radiotherapy is reserved for those with residual or more extensive disease, so its apparent "benefit" often simply marks more favorable tumor biology in patients who did not need it. For example, Ren et al. (2014) reported that overall survival in endometrial cancer patients undergoing salvage surgery depended strongly on how much of the tumor was removed. They also suggested that the choice of adjuvant therapy was more related to how widespread the disease was, rather than having a direct effect on survival. (37) Therefore, the lack of a clear benefit of radiotherapy in our analysis does not mean it is unimportant, it may simply reflect that its use is closely linked to disease extent and surgical results.

Our examination of preoperative predictors yielded mixed results. In the FIGO IV cohort, elevated BMI was significantly associated with worse survival ($p = 0.039$), whereas other factors (age, FIGO substage IVB vs IVA, histology, grade, presence of metastases) showed no significant effect. Obesity is a well-known risk factor for endometrial cancer development, but its prognostic impact in the setting of advanced disease is less well-defined. Our finding suggests that very high BMI may impair outcomes, potentially through surgical risk or metabolic milieu, although this is not widely reported in the literature on stage IV debulking.

In the recurrent cohort, none of the preoperative variables reached statistical significance for survival, though histology showed a trend ($p = 0.056$). Endometrioid tumors tended to do better than non-endometrioid, consistent with the literature. Moukarzel et al. (2021) found that younger age (<70 years) and endometrioid histology were associated with improved post-recurrence survival after secondary cytoreduction. They even proposed preliminary selection criteria for secondary cytoreductive surgery (SCS) based on retrospective analysis. Patients with favorable prognostic characteristics - such as age ≤ 70 years, early-stage disease at initial diagnosis, grade 1/2 endometrioid or clear cell histology, no residual disease after primary surgery, and a solitary site of recurrence - were found to derive the greatest survival benefit from surgical intervention. Conversely, factors such as BMI at diagnosis, use of adjuvant chemotherapy, and size or location of the recurrent tumor did not significantly differ between surgical and non-surgical cohorts and may be of lesser importance in guiding treatment selection. (31)

Shikama et al. (2019) identified endometrioid histology (and good performance status) as independent predictors of longer survival following salvage surgery. (32) In our series the effect of histology did not reach conventional significance, likely due to sample size, but its borderline p-value and its recurrence in other studies suggest it may indeed be clinically relevant. Other factors that have been linked to optimal resection - such as small tumor size, solitary recurrence, and younger age - were not consistently identified as prognostic in our analysis. However, Ren et al. (2014) found that exactly those features (tumor ≤6 cm, solitary site, age ≤56) predicted the ability to achieve optimal cytoreduction and thus better survival. It is likely that our analysis was underpowered to detect a statistically significant difference, but the consistent trend suggests that selection of surgical candidates, such as those with limited disease and good performance status, remains critical. Other factors identified in the literature that favor better outcomes after surgery include younger age, endometrioid histology, and absence of bulky extrauterine disease. (38)

It is noteworthy that surgical approach (minimally invasive vs open) was not associated with poorer survival. In our cohort, patients selected for laparoscopic cytoreduction did not experience inferior outcomes compared to laparotomy, and this agrees with existing evidence in gynecologic oncology. Notably, Kim et al. (2021) compared advanced-stage patients treated by laparotomy versus MIS and found a significantly higher recurrence rate with open surgery (43.1% vs. 25.8%, p = 0.033), lower disease-free survival in the open group (p = 0.029), and no significant difference in overall survival. In their cohort, MIS was actually associated with better outcomes, possibly reflecting lower perioperative morbidity and faster recovery. (39) These findings echo other reports that modern minimally invasive techniques yield comparable long-term survival with less blood loss and shorter hospital stays. Although direct literature on MIS cytoreduction in the setting of bulky stage IV or recurrent disease is limited, available data suggest MIS can achieve similar oncologic results when complete resection is feasible. Fader et al. (2012) and Gao et al. (2015) likewise reported that laparoscopic or robotic-assisted staging and resection in high-risk endometrial cancer did not compromise survival compared to laparotomy while providing the known benefits of MIS (reduced complications, shorter stay). (40, 41)

However, the role of lymphadenectomy remains controversial. In this study, lymph node dissection did not show a significant survival benefit in the FIGO IV cohort, and its prognostic relevance in the recurrent setting is limited due to prior surgical treatment. Fader et al (2012) indicate that the MIS cohort had a higher mean lymph node count (39.0 vs. 34.0; p = 0.03) (41), while other studies showed that para-aortic lymphadenectomy was performed more frequently in the open surgery group, which also had a significantly higher number of lymph nodes removed. (39, 42). In contrast to Gao et al. (2015), who reported that the number of para-aortic lymph nodes removed was comparable between the laparoscopy and laparotomy groups, while the pelvic lymph node count was notably lower in patients who underwent laparoscopy. (40)

In summary, our analysis contributes to the growing body of evidence suggesting that surgery offers meaningful benefit in carefully selected patients, even in the context of advanced or disseminated disease. By stratifying patients into FIGO IV and recurrence cohorts and analyzing treatment modalities alongside preoperative clinical variables, the study provides a differentiated perspective on surgical outcomes and supports the hypothesis that maximal tumor debulking improves prognosis.

Other prognostic factors, such as BMI in stage IV or histology in recurrence, may modulate outcomes, but they appear secondary to the overriding effect of surgical clearance.

In practical terms, this means that a multi-disciplinary team should evaluate FIGO IV or recurrent patients to identify those who can safely achieve maximal resection. Patients with good performance status, limited metastatic spread, and favorable histology should be counseled that surgery may prolong survival, whereas for others, the role of surgery must be weighed against expected morbidity.

It should also be noted that the data analyzed in this study were collected before immunotherapy became part of standard care for endometrial cancer. In recent years, checkpoint inhibitors such as pembrolizumab, dostarlimab, and durvalumab have shown promising results. These treatments may offer an effective alternative to surgery in selected patients or change the timing and indication for surgical intervention. Therefore, the role of cytoreductive surgery could shift in the future as these systemic therapies become more established. Future research should explore how best to integrate surgery with modern immunotherapies to optimize outcomes for each individual patient.

To better understand the future role of surgery, further clinical data are needed that take these new treatment options into account. Our findings support the need for such investigations, particularly regarding optimal patient selection. Additionally, as minimally invasive techniques evolve, more data are needed on long-term oncologic outcomes of laparoscopic or robotic cytoreduction in this context.

Limitations:

This study has several limitations that should be considered when interpreting the results. First, due to its retrospective design, the analysis is subject to inherent biases, including selection and information bias. Surgical decisions were not randomized and may have been affected by clinical factors such as performance status, comorbidities, or tumor burden, which the dataset could not fully account for.

Second, the relatively small sample size (n = 79), particularly within the subgroups, limits statistical power and increases the risk of type II error, meaning that a true effect may remain undetected due to the small sample size. Given that the majority of endometrial cancer presents at an early stage, the number of patients with advanced or recurrent disease eligible for inclusion was inherently limited. Subgroup analyses, especially within the operated cohort, were based on small numbers (e.g. only 16 patients with stage IV disease and surgery), which can result in unreliable estimates and make it harder to apply the findings to a larger population.

Moreover, the overlap between patients with stage IV disease and recurrent disease (n = 7) complicates clear group allocation and interpretation. Although efforts were made to categorize patients based on their clinical presentation, potential misclassification bias cannot be ruled out.

Additionally, overall survival data must be interpreted with caution. Since data collection ended in July 2024, the last follow-up was limited to that date, potentially underestimating survival times in censored patients. Furthermore, the cause of death could not always be definitively attributed to endometrial cancer. In one case, a patient died following a fall from a window in a suicide attempt, highlighting the challenge of determining cancer-specific mortality in a retrospective setting.

Finally, as a single-center study, external validity is limited. The findings may not be directly transferable to other institutions or patient populations with differing treatment protocols or surgical expertise.

References

1. Fund WCR. Endometrial cancer statistics n.d [Available from: https://www.wcrf.org/preventing-cancer/cancer-statistics/endometrial-cancer-statistics/.
2. Barlin JN, Puri I, Bristow RE. Cytoreductive surgery for advanced or recurrent endometrial cancer: a meta-analysis. Gynecol Oncol. 2010;118(1):14-8.
3. Society TAC. Survival Rates for Endometrial Cancer n.d. [Available from: https://www.cancer.org/cancer/types/endometrial-cancer/detection-diagnosis-staging/survival-rates.html.
4. Tronconi F, Nero C, Giudice E, Salutari V, Musacchio L, Ricci C, et al. Advanced and recurrent endometrial cancer: State of the art and future perspectives. Crit Rev Oncol Hematol. 2022;180:103851.
5. Crosbie EJ, Kitson SJ, McAlpine JN, Mukhopadhyay A, Powell ME, Singh N. Endometrial cancer. Lancet. 2022;399(10333):1412-28.
6. Zanfagnin V, Ferrero A, Biglia N, Aletti G, Gill SE, Makdisi PB, et al. The role of surgery in recurrent endometrial cancer. Expert Rev Anticancer Ther. 2016;16(7):741-50.
7. Berek JS, Matias-Guiu X, Creutzberg C, Fotopoulou C, Gaffney D, Kehoe S, et al. FIGO staging of endometrial cancer: 2023. Int J Gynaecol Obstet. 2023;162(2):383-94.
8. Gaffney D, Matias-Guiu X, Mutch D, Scambia G, Creutzberg C, Fotopoulou C, et al. 2023 FIGO staging system for endometrial cancer: The evolution of the revolution. Gynecol Oncol. 2024;184:245-53.
9. Bosse T, Nout RA, McAlpine JN, McConechy MK, Britton H, Hussein YR, et al. Molecular Classification of Grade 3 Endometrioid Endometrial Cancers Identifies Distinct Prognostic Subgroups. Am J Surg Pathol. 2018;42(5):561-8.
10. Schwameis R, Fanfani F, Ebner C, Zimmermann N, Peters I, Nero C, et al. Verification of the prognostic precision of the new 2023 FIGO staging system in endometrial cancer patients - An international pooled analysis of three ESGO accredited centres. Eur J Cancer. 2023;193:113317.
11. Leon-Castillo A, de Boer SM, Powell ME, Mileshkin LR, Mackay HJ, Leary A, et al. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. 2020;38(29):3388-97.
12. Zammarrelli WA, 3rd, Kim SH, Da Cruz Paula A, Rios-Doria EV, Ehmann S, Yeoshoua E, et al. Risk Stratification of Stage I Grade 3 Endometrioid Endometrial Carcinoma in the Era of Molecular Classification. JCO Precis Oncol. 2022;6:e2200194.
13. Hohn AK, Brambs CE, Hiller GGR, May D, Schmoeckel E, Horn LC. 2020 WHO Classification of Female Genital Tumors. Geburtshilfe Frauenheilkd. 2021;81(10):1145-53.
14. Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S, et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. Int J Gynecol Cancer. 2021;31(1):12-39.
15. Anglesio MS, Wang YK, Maassen M, Horlings HM, Bashashati A, Senz J, et al. Synchronous Endometrial and Ovarian Carcinomas: Evidence of Clonality. J Natl Cancer Inst. 2016;108(6):djv428.
16. Schultheis AM, Ng CK, De Filippo MR, Piscuoglio S, Macedo GS, Gatius S, et al. Massively Parallel Sequencing-Based Clonality Analysis of Synchronous Endometrioid Endometrial and Ovarian Carcinomas. J Natl Cancer Inst. 2016;108(6):djv427.
17. Matsuo K, Klar M, Song BB, Roman LD, Wright JD. Validation of the 2023 FIGO staging schema for advanced endometrial cancer. Eur J Cancer. 2023;193:113316.
18. Li H, Zhang R, Chen C, Wu C, Lin H, Li J, et al. Prognostic value of different metastatic sites for patients with FIGO stage IVB endometrial cancer after surgery: A SEER database analysis. J Surg Oncol. 2020;122(5):941-8.
19. Bokhman JV. Two pathogenetic types of endometrial carcinoma. Gynecol Oncol. 1983;15(1):10-7.
20. Murali R, Soslow RA, Weigelt B. Classification of endometrial carcinoma: more than two types. Lancet Oncol. 2014;15(7):e268-78.

21. Westphal DK. Den Überblick behalten – Therapie des fortgeschrittenen/rezidivierenden Endometriumkarzinoms 2024 [Available from: https://www.springermedizin.de/endometriumkarzinom/endometriumkarzinom/sonderbericht-therapie-des-fortgeschrittenen-rezidivierenden-ec/26660862?searchResult=3.zielgerichtete%20therapien%20beim%20rezidivierenden%20Endometriumkarzinom&searchBackButton=true.
22. N. Pauly PDBA. Zielgerichtete Therapien beim rezidivierten Endometriumkarzinom 2: Moderne Ansätze: Springer Medizin; 2023 [Available from: https://www.springermedizin.de/endometriumkarzinom/zytostatische-therapie/zielgerichtete-therapien-beim-rezidivierten-endometriumkarzinom-/23953178#CR15_source_0.
23. Mahdi H, Chelariu-Raicu A, Slomovitz BM. Immunotherapy in endometrial cancer. Int J Gynecol Cancer. 2023;33(3):351-7.
24. Wada M, Yamagami W. Immunotherapy for endometrial cancer. Int J Clin Oncol. 2025;30(3):449-56.
25. Bogani G, Monk BJ, Powell MA, Westin SN, Slomovitz B, Moore KN, et al. Adding immunotherapy to first-line treatment of advanced and metastatic endometrial cancer. Ann Oncol. 2024;35(5):414-28.
26. Reynolds S. More Immunotherapy Options Approved for Treating Endometrial Cancer: National Cancer Institute; 2024 [Available from: https://www.cancer.gov/news-events/cancer-currents-blog/2024/endometrial-cancer-durvalumab-pembrolizumab-chemotherapy.
27. Goff BA, Goodman A, Muntz HG, Fuller AF, Jr., Nikrui N, Rice LW. Surgical stage IV endometrial carcinoma: a study of 47 cases. Gynecol Oncol. 1994;52(2):237-40.
28. Chi DS, Welshinger M, Venkatraman ES, Barakat RR. The role of surgical cytoreduction in Stage IV endometrial carcinoma. Gynecol Oncol. 1997;67(1):56-60.
29. Kanno M, Yunokawa M, Kurihara N, Aoki Y, Omi M, Tanigawa T, et al. Efficacy of intra-abdominal cytoreductive surgery in advanced endometrial cancer with distant metastasis. J Gynecol Oncol. 2023;34(6):e77.
30. Bristow RE, Santillan A, Zahurak ML, Gardner GJ, Giuntoli RL, 2nd, Armstrong DK. Salvage cytoreductive surgery for recurrent endometrial cancer. Gynecol Oncol. 2006;103(1):281-7.
31. Moukarzel LA, Braxton KF, Zhou QC, Pedra Nobre S, Iasonos A, Alektiar KM, et al. Non-exenterative surgical management of recurrent endometrial carcinoma. Gynecol Oncol. 2021;162(2):268-76.
32. Shikama A, Minaguchi T, Takao W, Hosokawa Y, Nishida K, Tasaka N, et al. Predictors of favorable survival after secondary cytoreductive surgery for recurrent endometrial cancer. Int J Clin Oncol. 2019;24(10):1256-63.
33. Ayhan A, Taskiran C, Celik C, Yuce K, Kucukali T. The influence of cytoreductive surgery on survival and morbidity in stage IVB endometrial cancer. Int J Gynecol Cancer. 2002;12(5):448-53.
34. Bristow RE, Zerbe MJ, Rosenshein NB, Grumbine FC, Montz FJ. Stage IVB endometrial carcinoma: the role of cytoreductive surgery and determinants of survival. Gynecol Oncol. 2000;78(2):85-91.
35. Scarabelli C, Campagnutta E, Giorda G, DePiero G, Sopracordevole F, Quaranta M, et al. Maximal cytoreductive surgery as a reasonable therapeutic alternative for recurrent endometrial carcinoma. Gynecol Oncol. 1998;70(1):90-3.
36. Campagnutta E, Giorda G, De Piero G, Sopracordevole F, Visentin MC, Martella L, et al. Surgical treatment of recurrent endometrial carcinoma. Cancer. 2004;100(1):89-96.
37. Ren Y, Shan B, Shi D, Wang H. Salvage cytoreductive surgery for patients with recurrent endometrial cancer: a retrospective study. BMC Cancer. 2014;14:135.
38. Fang C, Zhang Y, Zhang P, Zhu T. Prognostic factors of patients with recurrent uterine malignancies undergoing secondary cytoreductive surgery. BMC Womens Health. 2024;24(1):9.
39. Kim SI, Park DC, Lee SJ, Yoo JG, Song MJ, Kim CJ, et al. Minimally invasive surgery for patients with advanced stage endometrial cancer. Int J Med Sci. 2021;18(5):1153-8.

40. Gao H, Zhang Z. Laparoscopy Versus Laparotomy in the Treatment of High-Risk Endometrial Cancer: A Propensity Score Matching Analysis. Medicine (Baltimore). 2015;94(30):e1245.
41. Fader AN, Seamon LG, Escobar PF, Frasure HE, Havrilesky LA, Zanotti KM, et al. Minimally invasive surgery versus laparotomy in women with high grade endometrial cancer: a multi-site study performed at high volume cancer centers. Gynecol Oncol. 2012;126(2):180-5.
42. Koskas M, Jozwiak M, Fournier M, Vergote I, Trum H, Lok C, et al. Long-term oncological safety of minimally invasive surgery in high-risk endometrial cancer. Eur J Cancer. 2016;65:185-91.