Synopsis

TITEL	Evaluation of preoperative clinical and translation selection criteria for cytoreductive surgery in endometrial cancer - A retrospective multicenter trial with an accompanying translational project
STUDY CODE	**AGO-OP.11/ ENGOT-en22/ STREAM-I** **S**urgical **Tr**eatment in Advanced and **R**ecurrent **E**ndometrial C**A**ncer **M**anagement
SPONSOR	AGO Research GmbH, AGO Study Group
COOPERATION	Institute of Pathology Ludwig-Maximilians-University (LMU)
COORDINATING INVESTIGATOR	Prof. Dr. med. Fabian Trillsch
INDICATION	Advanced or recurrent endometrial carcinoma
RATIONALE	Endometrial cancer (EC) is the most common gynecological cancer in Europe with an incidence of about 73.000 in 2020 [1]. In Germany, a relative 10-year survival rate of 74% is estimated [2]. At first diagnosis, approximately 20% are already in advanced stages (FIGO III-IV) and up to 15% of the patients will relapse significantly impairing prognosis with an estimated 5-year survival rate of only 17% [3-5]. While in ovarian cancer cytoreductive surgery (CRS) is considered as standard treatment approach at first diagnosis and in case of relapse, reliable data regarding CRS in advanced and recurrent EC is missing and the indication for CRS is widely based on an individual case selection [6]. In general, the rationale for CRS in ovarian cancer may also apply for advanced EC. Residual tumor lesions with areas of poorly vascularized cells may be hard to access for systemic treatment but can be removed by CRS. Remaining tumor tissue, in contrast, would require higher doses of chemotherapy and could be a source for a later chemoresistance. By decreasing tumor size, the host immune system can be activated and could have specific significance in EC, which is often described as an immunogenic cancer [7]. Until now, only few studies exist regarding CRS in advanced and recurrent EC. Mostly single-center, retrospective studies showed an advantage by CRS, but all studies had only small patient groups and a range between 18-75% for complete cytoreduction was described depending on the FIGO stage and other, mostly unknown factors [8-14]. Generating a robust base for evaluating the impact of CRS in advanced EC appears very important to improve the evidence for treatment decisions in clinical routine.

	Establishing hypotheses and a specific score based on clinical characteristics to identify patients who are most likely to benefit from a radical surgical approach could be a promising perspective for upcoming prospective trials on CRS in advanced EC. Recently, new subgroups of endometrial cancer have been established using molecular classifications based on The Cancer Genome Atlas (TCGA) database, that provide additional prognostic factors and help tailoring therapeutic strategies on a translational base [15]. For recurrent disease, it was shown that patients with tumors exhibiting mismatch repair deficiency (dMMR) significantly benefit from immunotherapy with PD-1 inhibitors but information on surgical impact of this molecular classification is completely missing. So far, trials solely focused on patients with measurable disease and all patients had to have received prior platinum-based chemotherapy. Following complete cytoreduction, however, patients are also candidates for postoperative treatment given the intraabdominal distribution without clear resection margins. Molecular classifications may give further information and selection criteria for CRS as well as for the systemic treatment following complete cytoreduction which could be beneficial for patients given potential side effects of both treatment modalities. Therefore, the role of CRS in advanced and relapsed EC will be evaluated in this international multi-center, retrospective study within the European Network for Gynaecological Oncological Trial groups (ENGOT), initiated and led by the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) study group. Following further development of the protocol within the Gynaecological Cancer Academy (GCA) workshop in December 2022 for a European and future perspective, European high-volume cancer centers surgically treating patients with advanced or relapsed EC will include their patient data to generate a profound database for this specific cohort of patients. Retrospective clinical data collection will be accompanied by a translational approach for patients with availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue.
STUDY DESIGN	European, open, retrospective descriptive, non-interventional, multicenter study
TARGET POPULATION	Adult patients who underwent cytoreductive surgery in European cancer centers for advanced endometrial cancer with peritoneal metastases (FIGO IV) or for recurrent endometrial cancer
OBJECTIVES	Establishing hypotheses and specific selection criteria based on clinical and/or translational characteristics to identify patients who are most likely to benefit from radical

	cytoreduction approach. i.e., complete resection, which could serve as a base for upcoming prospective trials on cytoreductive surgery in endometrial cancer. **Primary objective** – Identification of clinical selection criteria to predict complete cytoreduction in patients with advanced or recurrent endometrial cancer **Secondary objectives** *Clinical part:* – Evaluation of prognostic factors predicting benefit from cytoreductive surgery in advanced or recurrent endometrial cancer – Identification of prognostic markers for the clinical outcome *Translational part:* – Evaluating the predictive value of the molecular classification according to TCGA for surgical outcome in endometrial cancer – Identification of biologic and molecular expression profiles to predict complete cytoreduction in patients with endometrial cancer and their prognostic significance **Exploratory objectives** Description of current treatment practices in participating European countries for advanced or recurrent endometrial cancer
INCLUSION CRITERIA	1. Patient underwent cytoreductive surgery (CRS) between 01/2011 and 12/2020 2. Patient's age at CRS ≥18 years 3. One of the following criteria has to be fulfilled: a. Primary diagnosis of advanced endometrial cancer and peritoneal metastases (FIGO IV) undergoing cytoreductive surgery OR b. Diagnosis of recurrent endometrial cancer undergoing cytoreductive surgery Optional but strongly encouraged for translational part: availability of FFPE tumor material from cytoreductive surgery
EXCLUSION CRITERIA	1. Patients with past medical history interfering with radical cytoreductive surgery 2. Patients undergoing surgery solely for palliative intent

	3. Patients with secondary malignancies requiring abdominal surgical treatment
INTERVENTION INVESTIGATIONS	None. Data will be collected retrospectively. Providing existing FFPE tumor blocks from cytoreductive surgery and documentation of patient characteristics and prior treatment modalities.
STUDY DURATION	Data and sample collection of the retrospective cases will be over a time period of 18 months.
VARIABLES AND OUTCOMES	▪ Baseline: Demographics Disease characteristics Medical history ▪ Primary disease: Tumor data Therapeutic data ▪ Recurrent disease: Localization Therapeutic data ▪ Outcome and survival data ▪ FFPE tumor blocks from cytoreductive surgery: a. expert pathological review and molecular classification b. establishment of TMAs c. DNA/RNA isolation for translational research Detailed variables are listed in chapter **Fehler! Verweisquelle konnte nicht gefunden werden.**
STATISTICAL ANALYSIS	Primary analysis: ▪ A multiple logistic regression of complete resection on clinical potentially predictive covariates will be established using a stepwise covariate selection. Secondary analyses: ▪ Multiple logistic regression of complete resection on clinical and translational covariates. ▪ Multiple Cox regressions of progression-free and overall survival on clinical and/or translational covariates.

References

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