Clínica Universidad de Navarra

Protocol Title

SUROVA-Surgery in Ovarian cancer

Full Protocol Title

An international worldwide retrospective cohort observational study comparing primary cytoreductive surgery with neoadjuvant chemotherapy and interval cytoreductive surgery in patients with carcinoma of the ovary, fallopian tubes, and peritoneum.

Indication

Ovarian Cancer Stage FIGO IIIB-IVB (FIGO 2018).

Chairman

Luis M. Chiva. MD, PhD.

Director of Department of Obstetrics and Gynecology

Co-Chairman

Pilar Ordás. PhD, Master in Genetics, Master in Big Data.

Trial Committee

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Study design

International, multicenter, observational, retrospective, cohort study of consecutive ovarian cancer cases operated in 2018 and 2019 within hospitals around the world that meet the inclusion-exclusion criteria. We plan to balance both groups by means of a *Propensity Score Matched Cohort Study*, *Inverse Probability weighting* and *Artificial Intelligence* for the variables that show statistical significance in the univariate and multivariate analysis.

Primary endpoint

Compare overall survival (OS) at 5 years in patients who underwent primary cytoreductive surgery vs. neoadjuvant chemotherapy and interval cytoreductive surgery for stage IIIB-IVB ovarian cancer.

Secondary endpoints

Progression Free Survival (PFS) at 5 years.

Time to first and second subsequent anticancer therapy or death.

Gather information on surgical treatment approaches and decision-making processes for patients with advanced high-grade ovarian cancer in worlwide centers.

Extend the surgery according to the Aletti surgical complexity score.

Documentation of surgical complications.

Compare the outcomes between patients with BRCA mutations and those without this mutation.

Compare the outcomes between patients with HRD deficiency and those with HRD proficiency.

Definitions

Overall survival is defined as the time from the first treatment (chemotherapy in the case of neoadyuvant chemotherapy and cytoreduction in the case of primary cytoreductive surgery) to death from ovarian cancer or last follow up.

Progression-free survival (PFS) is defined as the time from the first treatment (chemotherapy in the case of neoadyuvant chemotherapy and cytoreduction in the case of primary cytoreductive surgery) to progressive disease or death, whichever occurs first or date of last contact (censored observation). Progressive disease is defined as clinical or imaging-detected tumor progression or death in cases without prior documented tumor progression.

Progression-free survival 2 (PFS2): PFS2 time is calculated from the date of the first treatment (chemotherapy in the case of neoadyuvant chemotherapy and cytoreduction in the case of primary cytoreductive surgery) until the date of second progressive disease or death, whichever occurs first or date of last contact (censored observation).

Time to first subsequent anticancer therapy or death (TFST): time to first subsequent anticancer therapy is calculated from the date of first treatment (chemotherapy in the case of neoadyuvant chemotherapy and cytoreduction in the case of primary cytoreductive surgery) until the starting date of the first subsequent anticancer therapy or death, whichever occurs first or date of last contact (censored observation). Maintenance treatments following a cytostatic treatment are not considered separate treatment lines.

Time to second subsequent anticancer therapy or death (TSST): time to second subsequent anticancer therapy is calculated from the date of first treatment (chemotherapy in the case of neoadyuvant chemotherapy and cytoreduction in the case of primary cytoreductive surgery) until the starting date of the second subsequent anticancer therapy or death, whichever occurs first or date of last contact (censored observation). Maintenance treatments following a cytostatic treatment are not considered separate treatment lines.

Background and Rationale

Cytoreductive surgery to achieve complete resection has been the standard treatment for patients with advanced ovarian cancer for the past decades, followed by chemotherapy. In the last years, the European Organisation for Research and Treatment of Cancer-Gynaecological Cancer Group (EORTC-GCG) and the National Cancer Institute of Canada Clinical Trials Group (NCIC) reported an alternative approach, involving initiating with neoadjuvant chemotherapy followed by interval cytoreductive surgery. However, the optimal strategy for patients with advanced ovarian cancer remains an ongoing debate and a topic of controversy worldwide, as reflected by the highly variable practices at both national and international levels.

While the prospective Trust Trial, with results expected in 2024, is designed to address this question, a limitation of this study is that it is confined to patients treated in high-quality departments in ovarian cancer surgery. This limitation could introduce bias in the real-life results, as many patients may lack access to such high-level healthcare facilities.

Therefore, we consider it crucial to carry out a highly controlled worlwide retrospective study that allows us to extend the scope of this study to real life and to draw sufficient conclusions to make adequate decisions in research on the surgical treatment of advanced ovarian cancer. This study may add relevant real-life information to the results of the Trust Trial.

Ovarian cancer is the fourth most common gynecological cancer among women. It typically presents in an advanced stage and is the third leading cause of death in women with gynecological malignancies. Globally, 240,000 women are diagnosed with ovarian cancer each year, and with a five-year survival rate of less than 45%, it accounts for 150,000 deaths (4.2% of all female deaths), making it the seventh most common cancer and the eighth most common cause of cancer-related death among women.

Our goal is to obtain data from 4000 patients that underwent cytoreductive surgery in 2018 and 2019. Approximately 2000 patients per arm.

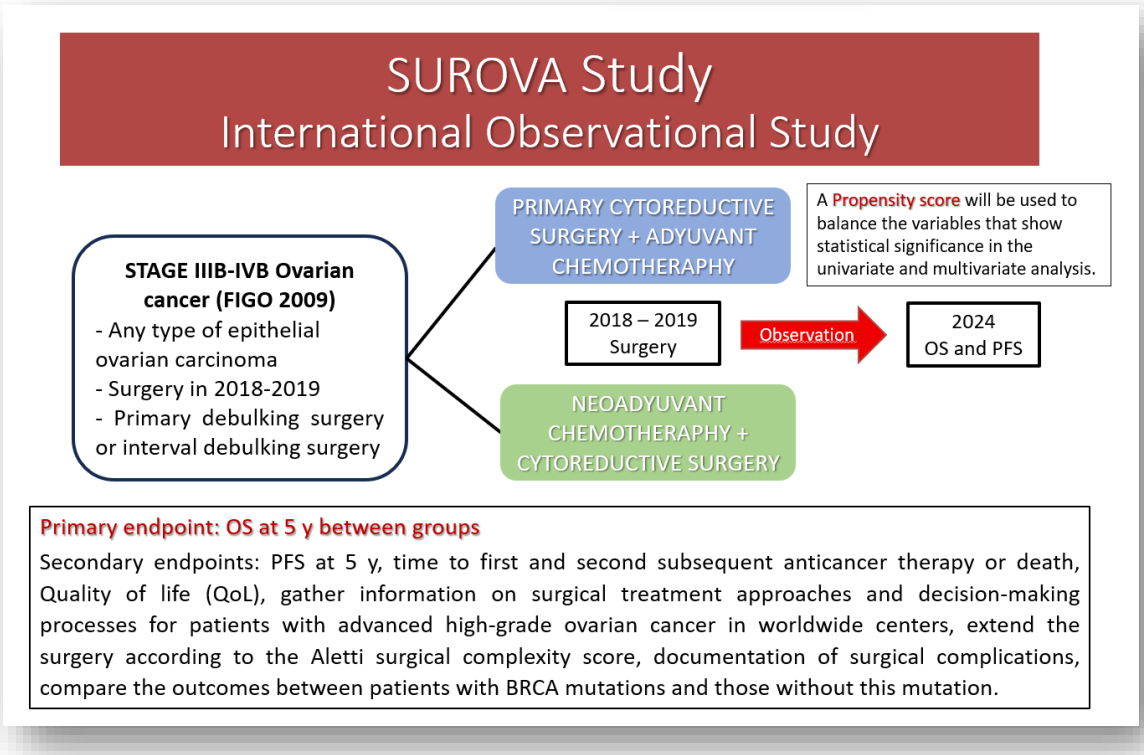
Scope of this study

• To take a real picture of what happened worldwide to those patients with IIIB-IVB ovarian cancer that underwent neoadyuvant chemotherapy followed by cytoreductive surgery instead of primary cytoreductive surgery.

• Compare outcomes after neoadyuvant chemotherapy followed by cytoreductive surgery vs primary cytoreductive surgery.

• Study risk factors for relapse.

• Determine the impact of the BRCA mutation and HRD deficiency.



Inclusion Criteria

- Patients >18 years old.
- ECOG Performance Status 0-1 at the time of the surgery.
- Invasive high-grade epithelial ovarian cancer, fallopian tube carcinoma, or primary peritoneal carcinoma in stage FIGO IIIB-IVB (IVB only if resectable metastases are present), suspected or histologically confirmed and newly diagnosed.
- Patient underwent primary surgery or first course of neoadyuvant chemotherapy between January 1, 2018, and December 31, 2019.
- ASA score 1 or 2 at the time of the surgery.

- Surgery performed by laparotomy with an attempt of maximal effort.
- The surgeon must be a certified or non-certified gynecologic oncologist.
- Based on all available information before the surgery (primary or interval), the patient was considered completely resectable.
- Adequate bone marrow function: Absolute neutrophil count (ANC) ≥ 1.5 x 109/L.
- Preoperative imaging (either CT, whole-body MRI, or PET-CT) excluding unresectable disease as per ESGO criteria.
- Surgical report on residual disease after surgery.

Exclusion Criteria

- Non-epithelial malignant ovarian neoplasms and borderline tumors.
- Secondary invasive neoplasms in the last 5 years (except synchronal endometrial carcinoma FIGO IA G1/2, non melanoma skin cancer, breast cancer T1 N0 M0 G1/2) or with any signs of relapse or activity.
- Recurrent ovarian cancer.
- Prior chemotherapy for ovarian cancer or abdominal/pelvic radiotherapy.
- Unresectable parenchymal lung metastasis, liver metastasis or bulky lymph-nodes in the mediastinum in CT chest and abdomen/pelvis before surgery (primary or interval).
- Pregnant women at the time of diagnosis.

Study Development

1. Submission to ESGO members the study application form.

2. Confirmation of participants to join the study and approval of the study by the Ethics Committee.

3. Accreditation of one Principal Investigator for each medical center and delivery of center codes.

4. Start collecting cases.

5. Deadline for collection of individual cases: Six months after the study release.

Screening for the candidate

How to participate in the study

1. Countries from around the world are allowed to participate in this study **(Appendix 1)**.

2. Fill and sign the **online application form** (see the link below) to accept the participation in the study as principal investigator (PI) of your institution (only one PI by each institution https://docs.google.com/forms/d/e/1FAIpQLSdoVQo3d1XnRbgUY4XsCd-lXRNnHdhJbeqQj7r0hPvvM0dhyA/viewform .

3. As soon as your center joins the study, you will receive a Center Identification code and e-mail with instructions, allowing the data collection.

4. Then, start to collect data of **consecutive ovarian cancer patients operated in 2018 and 2019** in your center that meet the inclusion and exclusion criteria. The success of this study is related to having data from all consecutive patients.

5. For collecting data, an online questionnaire will be provided.

6. Every time you submit a complete case form, you will receive an e-mail with the confirmation and a copy of your response. For sending the form, you have to fill at least the required items. You are allowed to re-edit your answers later.

1. We want to complete the data collection in less than six months.

2. As principal investigator, I will be available for any doubt by e-mail (lchiva@unav.es), or also by phone (+34630232947)

Data statistical management

A propensity score will be calculated to construct a weighted cohort of patients. For comparison of the distributions of categorical variables we will use the chi-square test in the unweighted cohort and weighted logistic-regression models in the weighted cohort. We will compare PFS and OS using the inverse probability of treatment–weighted log-rank test and plotted weighted survival functions and artificial intelligence. Estimation of the hazard ratio for death from any cause after primary cytoreductive surgery, as compared with cytoreductive surgery after neoadyuvant chemotherapy, with weighted Cox proportional-hazards models. Sensitivity analyses to assess the robustness of findings.

Data Publication

Hopefully, the results of this study will be submitted for evaluation to international meetings and publication in a relevant international journal. Authorship will include investigators following a strict criteria, considering the introduced number of cases in the study by each investigator. We will try to count on as many authors we may.

Furthermore, in order to count with as many authors as possible, we will create a **Surova Research Study Group** that will offer authorship as contributors when the investigators cannot be allocated among the first authors. At the time of the publication, we will follow the STROBE guidelines for observational studies. STROBE stands for an international, collaborative initiative of epidemiologists, methodologists, statisticians, researchers and journal editors involved in the conduct and dissemination of observational studies, with the common aim of STrengthening the Reporting of OBservational studies in Epidemiology.

Study registration

Surova Study is in process of registration at ClinicalTrials.gov.

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Appendix 1. Countries that are allowed to participate in this study

Afghanistan	Dominican Republic	Liechtenstein	Samoa
Albania	Ecuador	Lithuania	San Marino
Algeria	Egypt	Luxembourg	Sao Tome and Principe
Andorra	El Salvador	Madagascar	Saudi Arabia
Angola	Equatorial Guinea	Malawi	Senegal
Antigua and Barbuda	Eritrea	Malaysia	Serbia

Argentina	Estonia	Maldives	Seychelles
Armenia	Eswatini (fmr. "Swaziland")	Mali	Sierra Leone
Australia	Ethiopia	Malta	Singapore
Austria	Fiji	Marshall Islands	Slovakia
Azerbaijan	Finland	Mauritania	Slovenia
Bahamas	France	Mauritius	Solomon Islands
Bahrain	Gabon	Mexico	Somalia
Bangladesh	Gambia	Micronesia	South Africa
Barbados	Georgia	Moldova	South Korea
Belarus	Germany	Monaco	South Sudan
Belgium	Ghana	Mongolia	Spain
Belize	Greece	Montenegro	Sri Lanka
Benin	Grenada	Morocco	Sudan
Bhutan	Guatemala	Mozambique	Suriname
Bolivia	Guinea	Myanmar (formerly Burma)	Sweden
Bosnia and Herzegovina	Guinea-Bissau	Namibia	Switzerland
Botswana	Guyana	Nauru	Syria
Brazil	Haiti	Nepal	Taiwan
Brunei	Holy See	Netherlands	Tajikistan
Bulgaria	Honduras	New Zealand	Tanzania
Burkina Faso	Hungary	Nicaragua	Thailand
Burundi	Iceland	Niger	Timor-Leste
Cabo Verde	India	Nigeria	Togo
Cambodia	Indonesia	North Korea	Tonga
Cameroon	Iran	North Macedonia	Trinidad and Tobago
Canada	Iraq	Norway	Tunisia
Central African Republic	Ireland	Oman	Turkey
Chad	Israel	Pakistan	Turkmenistan
Chile	Italy	Palau	Tuvalu
China	Jamaica	Panama	Uganda
Colombia	Japan	Papua New Guinea	Ukraine
Comoros	Jordan	Paraguay	United Arab Emirates
Congo (Congo-Brazzaville)	Kazakhstan	Peru	United Kingdom
Costa Rica	Kenya	Philippines	United States of America
Côte d'Ivoire	Kiribati	Poland	Uruguay
Croatia	Kuwait	Portugal	Uzbekistan
Cuba	Kyrgyzstan	Qatar	Vanuatu
Cyprus	Laos	Romania	Venezuela
Czechia (Czech Republic)	Latvia	Russia	Vietnam
Democratic Republic of the Congo	Lebanon	Rwanda	Yemen

Denmark	Lesotho	Saint Kitts and Nevis	Zambia
Djibouti	Liberia	Saint Lucia	Zimbabwe
Dominica	Libya	Saint Vincent and the Grenadines	

Appendix 2. SUROVA STUDY application form

Application form for participation in this project as Principal Investigator (PI) in your institution

SURGERY IN OVARIAN CANCER (SUROVA)

A worlwide multicentric observational study

Cases of 2018 and 2019

PI. Luis Chiva MD PhD, CLINICA UNIVERSIDAD DE NAVARRA

* Required

Email address*

First name*

Last name*

Please specify your position: *
(*mark only one oval)*

- Physician attending
- Fellow
- Resident
- Other

In which country are you located? *

Name of your institution/hospital/cancer center *

City *

Address *

Zip code *

Telephone number *

Type of institution:
(*mark only one oval*)

- Academic public hospital
- Non Academic public hospital
- Academic private hospital
- Non Academic private hospital

On average, how many advanced epitelial ovarian cancer do you operate every year in your institution?
(make ony one oval)

- Less than 5
- 5-10
- 10-20
- 20-30
- 30-40
- >40

Realistic number of cases that might be included?

Any comments or suggestions to the study?

I wish to participate in Surova study
Signed (write down your name)