Patient Outcomes following Interval and Delayed Cytoreductive Surgery in Advanced Ovarian Cancer: protocol for a multicentre, international, cohort study (Global Gynaecological Oncology Surgical Outcomes Collaborative)

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Word count: 2015

ABSTRACT

Background

The Global Gynaecological Oncology Surgical Outcomes Collaborative has developed a network of gynaecological oncology surgeons, surgical departments and other interested parties that have the long-term ability to collaborate on outcome studies. Presented is the protocol for the GO SOAR2 collaborative study.

Primary objectives

To compare survival following interval and delayed cytoreductive surgery; between delayed cytoreductive surgery and no surgery (chemotherapy alone); and international variations in access to cytoreductive surgery for women with stage III-IV epithelial ovarian cancer.

Hypotheses

There is no difference in survival following interval and delayed cytoreductive surgery; there is poorer survival with no surgery compared to delayed cytoreductive surgery; and there are international disparities in prevalent practice and access to cytoreductive surgery in women with stage III-IV epithelial ovarian cancer.

Trial design

International, multi-centre, mixed methods cohort study. Participating centres, will review medical charts/electronic records of patients who had been consecutively diagnosed with stage III-IV ovarian cancer between January 1st 2006 and December 31st 2021. Qualitative interviews will be conducted to identify factors determining international variations in access to cytoreductive surgery.

Major inclusion/exclusion criteria

Inclusion criteria include women with stage III-IV epithelial ovarian cancer, undergoing interval (after 3-4 cycles of chemotherapy) or delayed (≥5 cycles of chemotherapy) cytoreductive surgeries or no cytoreductive surgery (≥5 cycles of chemotherapy alone).

Primary endpoints

Overall survival (defined from date of diagnosis to date of death); progression free survival (defined from date of diagnosis to date of first recurrence); facilitator/barriers to prevalent practice and access to cytoreductive surgery.

Sample size

In order to determine whether there is a difference in survival following interval and delayed cytoreductive surgery and no surgery, data will be abstracted from 1000 patients.

Estimated dates for completing accrual and presenting results

It is estimated recruitment will be completed by 2023 and results published by 2024.

Trial registration

ClinicalTrials.gov registry: NCT05523804

INTRODUCTION

The standard of care for advanced epithelial ovarian cancer is primary cytoreductive surgery with the aim for macroscopic complete cytoreduction, followed by platinum and taxane-based chemotherapy and consideration of maintenance therapy (bevacizumab or a Poly ADP-ribose polymerase (PARP)-inhibitor). Neoadjuvant chemotherapy before and after interval cytoreductive surgery has become an alternative approach as randomized controlled trials demonstrated non-inferiority of this type of management over primary surgery in selected patients.[1] Indications include poor performance status and comorbidities resulting in contra-indication to surgery, radiological evidence of perceived unresectable sites of disease, or insufficient surgical resources particularly when high complexity surgery is required to achieve complete cytoreduction. The optimal duration of neoadjuvant chemotherapy is not yet established with three cycles being the standard of care. There is a paucity of data in the setting of extended use of neoadjuvant chemotherapy (more than four cycles). Data on the role of delayed cytoreductive surgery after more than four cycles are controversial. While some data have shown survival to be similar to that of patients undergoing interval cytoreductive surgery after three cycles,[2-8] others have reported poorer prognosis of delayed surgery.[9-12] Conflicting data are due to selection biases such as heterogeneous inclusion criteria, small sample sizes and retrospective study designs. There is also a paucity of data on survival outcomes comparing delayed cytoreduction surgeries to no surgery (neoadjuvant chemotherapy only).

The ongoing strain of the global COVID-19 pandemic on hospital resources has forced many centres to alter the timing of interval surgery and extend the number of neoadjuvant chemotherapy cycles. In addition, international disparities in access to surgical resources between high and low-middle income countries also results in delayed surgery or even no surgery. Therefore there is a pressing need to obtain clarity.

The Global Gynaecological Oncology Surgical Outcomes Collaborative (GO SOAR) has developed a network of gynaecological oncology surgeons, surgical departments, and other interested parties that have the long-term ability to collaborate on outcome studies.[13] A key objective of the collaborative is to understand disparities in access to surgical care and through collaborative research, inform and facilitate policy change to help reduce such disparities.[13]

We present the protocol for the second GO SOAR collaborative study (GO SOAR2) which compares survival following interval and delayed cytoreductive surgery, between delayed cytoreduction and no surgery, as well as investigating international variations in prevalent practice and access to cytoreductive surgeries. The full protocol has also been registered (NCT05523804).

Our hypotheses are that there is no difference in survival following interval and delayed cytoreductive surgery; there is poorer survival with no surgery and chemotherapy alone compared to delayed cytoreductive surgery; and there are international disparities in prevalent practice and access to cytoreductive surgery in women with stage III-IV epithelial ovarian cancer.

METHODS

Trial design

Study design is that of an international, multicentre, mixed method cohort study. There are forty sites planned (three currently active). The study has been approved and registered with the Quality Improvement & Assurance Team (QIAT) at NHS Grampian (project ID 5719), UK.

To ensure surgical outcome data collected are representative of care received in each country, attempts will be made to recruit large/medium/small centres performing ovarian cancer cytoreductive surgery in a 1:1:1 ratio. Centres will be defined according to annual ovarian cancer cytoreduction surgical caseload as follows: large $\geq$100, medium 50-99, small 49-20 new surgical gynaecological cancer cases per annum. To be eligible to participate in the study, centres must be performing a minimum of 20 ovarian cancer cytoreduction surgeries per annum. Centre size thresholds have been set in accordance with European Society of Gynaecological Oncology quality indicators for advanced ovarian cancer surgery.[14] Figure 1 summarises the study schema.

Participating centres, will review medical charts/electronic records of patients who had been consecutively diagnosed with stage III-IV epithelial ovarian cancer between January 1st 2006 and December 31st 2021. Selecting at start date of 2006 will help identify changes in prevalence practice of delayed cytoreductive surgeries and how this has evolved over the course of the last fifteen years. Qualitative semi-structured in-depth interviews will be conducted with all participating centres to identify factors determining international variations in prevalent practice and access to cytoreductive surgery. Data will not be presented at the level of individual surgeon/site, but instead be evaluated within the context of high income versus low and middle income country settings as defined by the World Bank.

To ensure high data quality, a standardised data collection template together with a detailed protocol has been produced and published online. Training is available to collaborators prior to the commencement of data collection and entry.

Data validation is completed in three stages across a representative sample of centres. First, centres self report key processes used to identify and follow-up patients. Second, independent validators locally not part of the recruiting teams quantitatively report case ascertainment and sampled data accuracy. Third, local teams are interviewed by the central coordinating team to qualitatively assess collaborator engagement and data collection processes.

Participants

Inclusion criteria include women with stage III-IV epithelial ovarian cancer, undergoing interval (after 3-4 cycles of chemotherapy) or delayed (≥5 cycles of chemotherapy) cytoreductive surgery or no cytoreductive surgery with chemotherapy alone (≥5 cycles of chemotherapy). Women undergoing primary and recurrent cytoreductive surgery are excluded as well as non-epthelial ovarian cancer histopathological subgroups. Data will be collected on indications for performing interval/delayed cytoreductive surgery and no surgery (chemotherapy alone). This is to ensure comparisons are made between similar patient cohorts.

Outcomes

The primary objectives of GO SOAR2 are to compare survival after interval and delayed cytoreductive surgeries; between delayed cytoreductive and no surgery; and international variations in prevalent practice and access to interval and delayed cytoreductive surgery. Secondary objectives include post-operative morbidity and disease resectability. Primary endpoints are overall survival (defined from date of diagnosis to date of death); progression free survival (defined from date of diagnosis to date of first recurrence); and facilitators/barriers to prevalent practice and access to interval/delayed cytoreduction surgery. Secondary endpoints include post-operative morbidity and tumour resectability rates. Post-operative morbidity will be defined as per the Clavien-Dindo

classification for surgical complications. Resectability will be defined as a measure of residual disease after surgery: R0 (no macroscopic residual disease), R1 (macroscopic residual disease with a maximal diameter of <1 cm), and R2 (macroscopic residual disease with a maximal diameter of >1 cm).

Sample size

For this retrospective study, we anticipate that a sample size of 1000 participants (333 in each group: interval cytoreductive surgery, delayed cytoreductive surgery, no surgery), from forty centres performing cytoreductive surgery with a fifteen year follow up, will be sufficient to achieve the number of events in each group. Event rate will be monitored and sample size adjusted accordingly if we find that a larger number of events are contributed by countries with a higher mortality rate.

In order to determine whether there is a difference in survival following interval and delayed cytoreductive surgery, we will require 114 events (deaths) to be recorded in each group. This is based on the assumptions that median survival in interval cytoreductive surgery group is 32 months and 47 months in the delayed cytoreductive surgery group; proportional hazards (that ratio of hazards between treatments (risks of death at fixed moment) is constant over time); power of 0.8; type I error rate of 0.05; and using a two-sided test. In order to determine whether there is worse survival with no surgery compared to delayed cytoreductive surgery, we will require 22 events to be recorded in each group. This is based on the assumptions that median survival in the delayed cytoreductive surgery group is 47 months and 21 months in the no surgery group; proportional hazards; power of 0.8; type I error rate of 0.05; and using a one-sided test.

The median survivals used in the power calculation have been determined using weighted means from published data.[2-12, 15-18] Current evidence on the survival following interval and delayed

cytoreductive surgery does not allow to produce a non-inferiority/equivalence sample size calculation to support our hypothesis that the survivals are equivalent. The weighted means calculated for the sample size calculation suggest a fifteen month survival benefit in favour of delayed cytoreductive surgery. Whilst the median survival for interval cytoreductive surgery is calculated from weighed means derived from robust randomised control study data, median survival for delayed cytoreductive surgery has been derived from small retrospective studies with sample sizes ranging from 29-318) which have a multitude selection biases. This however is all the available published data on delayed cytoreductive surgery. We believe however that the total sample number of participants would allow us to obtain more reliable estimate of corresponding survivals which we will use to test out hypothesis.

Statistical methods

Descriptive statistics will be calculated for baseline characteristics. Continuous variables will be summarised as median (Interquartile range (IQR)) and categorical as frequency (percentage). The chi-squared test of Fisher's exact test will be used for testing hypotheses on differences in proportions between groups. The Wilcoxon rank-sum test will be used for testing hypotheses on differences between groups. Multivariable logistic regression analysis will be performed to assess the association between the variables and survival, complications and resectability. Survival analysis using the Kaplan-Meier method (adjusted for age, ethnicity, performance status, resectability achieved, histopathology, *BRCA* mutation status, chemotherapy response score, income country setting (high versus low and middle income as defined by the World Bank), indication for delaying surgery or administering chemotherapy alone) will be performed and compared using the log-rank test. A p-value<0.05 will be considered as statistically significant. Cases lost to follow up will be censored. Statistical analysis will be performed using R version 3.5.1 (https://cran.r-project.org). Qualitative interviews will be analysed using an inductive theoretical framework. Progress on data

collection and summary statistics will be reported to the international steering committee at their regular meetings. Analysis of the full data set will be undertaken at the end of the study.

DISCUSSION

The GO SOAR Collaborative has implemented a series of internationally collaborative studies. This protocol describes the GO SOAR2 collaborative study which is a multicentre, mixed methodology, cohort study comparing survival after interval and delayed cytoreductive surgery; between delayed cytoreduction and no surgery with chemotherapy alone; and international variations in access to interval and delayed cytoreductive surgery. The role of delayed cytoreductive surgery in the management of advanced ovarian cancer is now more relevant than ever in light of delays in surgery caused by the COVID pandemic which has increased disparities in access to surgical resources.

Optimum cytoreduction is an independent marker of survival and should be the goal of all cytoreductive surgeries in ovarian cancer. Therefore, if optimum cytoreduction (R0, R1) is not achievable, surgery ought to be discontinued in favour of subsequent chemotherapy and maintenance therapy. Delaying surgery to after five cycles has the potential to reduce surgical complexity, reduce post-operative morbidity, increase the rate of complete cytoreduction, and increase the rate of pathological complete response. Of particular interest is how survival differs between delayed surgery compared to individuals who undergo no surgery and just five or more cycles of neoadjuvant chemotherapy due to persistent unresectable disease, poor performance status or severe comorbidities that are contraindications to surgery.

CHRONO is an ongoing, prospective, multicentre, French, randomized phase III trial aimed at assessing the impact of delayed surgery after six courses of neoadjuvant chemotherapy in patients

treated for advanced ovarian cancer.[19] The study is powered on progression free survival which is not a clinical efficacy endpoint (unlike overall survival). GO SOAR 2 will generate the largest international dataset on the impact of delayed surgery on overall survival.

Often research in gynaecological oncology takes place within high income country settings with recommendations difficult to implement in low-middle income countries with limited resources. Inclusion of low-middle income country partners are vital to be able to identify context specific solutions and to ensure high quality surgical care in a low resource setting.[13]

In conclusion, the GO SOAR2 study will be the largest international multicentre study comparing survival between interval and delayed cytoreductive surgery, and will generate novel survival data comparing delayed cytoreductive surgery to no surgery (neoadjuvant chemotherapy alone) whilst also generating insights into reasons for international disparities in access to surgical cytoreduction surgeries.

Contribution to authorship

Study conception and design: FG.

Protocol development: FG, NB, PR, PK, OB, IK, DC, SP, AJ, EB, AL, RM, JD, NG, JB, MN, TI, OH, DB.

Steering committee: FG, KA, PR, NB, PK, OB.

Study management: FG, KA, NB.

Preparation of figures: FG.

Initial draft of manuscript: FG.

Statistical aspects: FG, OB.

Manuscript writing and approval: All authors.

Disclaimers/Conflict of interest statement

FG declares funding from The NHS Grampian Endowment Fund, Medtronic, Karl Storz outside of this work and honorarium from Astra Zeneca. RM declares research funding from Barts Charity, Rose Trees Trust, Yorskshire Cancer Research, CRUK, Eve Appeal and honoraria from GSK, MSD, Astrazeneca and EGL outside this work. DC declares honorarium from Astra Zeneca. All other authors declare no conflict of interest.

Funding

The study is supported by the Grampian Endowment Fund.

Ethical approval

The study has been approved and registered with the Quality Improvement & Assurance Team (QIAT) at NHS Grampian (project ID 5719), UK.

Acknowledgements

We are grateful to the members of the international steering committee. We acknowledge support provided by a number stakeholders including the University of Aberdeen, European Network of Young Gynae Oncologists (ENYGO) and Target Ovarian Cancer.

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Figure 1: Study flowchart

FIGO – International Federation of Gynecology and Obstetrics.