**IS PRIMARY DEBULKING SURGERY AS EFFECTIVE AS INTERVAL DEBULKING FOR LOCALLY ADVANCED EPITHELIAL OVARIAN CANCER?**

Protocol of thesis submitted for partial fulfillment of MD in Surgical Oncology

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**INTRODUCTION**

Epithelial ovarian cancer (EOC) is the leading cause of death in women with gynecological malignancy [Ferlay*et al.,*2010]. The estimated annual incidence of EOC is 225,500 with an estimated 140,200 deaths worldwide in 2008, consisting of 3.7% of all female cancers and 4.2% of cancer deaths [World Health Organization, 2011]. Due to inadequate screening tools and a lack of early clinical symptoms, approximately 70% of women with EOC are diagnosed with advanced stage of disease, which is associated with high morbidity and mortality [Cannistra, 2004; Heintz*et al*. 2006;Jemal*et al*. 2010]. Currently, standard primary therapy for patients with advanced EOC is primary debulking surgery (PDS) aiming to remove all visible tumor tissue, followed by adjuvant chemotherapy (ACT) with paclitaxel and carboplatin [Du Bois *et al*. 2005; Du Bois and Pfisterer, 2005;Pignata*et al*. 2011].

Residual disease at the end of surgery is a major prognostic factor for survival [Winter *et al.* 2007], justifying, staging laparotomy and extensive cytoreductive surgery.Gynecologic oncologists perform a resection of disseminated disease by resecting the peritoneum and other organs such as the intestinal tract, liver and spleen. Over the last decade, the goal of advanced EOC debulking surgery has changed from residual tumor less than 1 cm to no macroscopic residual tumor both in primary debulking surgery and interval debulking surgery [Hoskins *et al.* 1992, 1994; Eisenkop*et al.* 1998; Vergote*et al.* 1998, 2010, 2011a; Bristow *et al.* 2002; Aletti*et al.* 2006; Chi *et al.* 2006, 2009; Winter *et al.* 2007; Du Bois *et al.* 2009].

However, complete resection of the tumor is often difficult for patients with massively disseminated tumors. EOC is one of the most sensitive of all solid tumors to cytotoxic drugs, with over 80% of women showing a response to standard chemotherapy combining taxane and platinum. Even if preoperative diagnostic imaging shows massive ascites and diffuse dissemination, these show a dramatic disappearance at IDS after NACT. Based on these clinical characteristics, NACT has been proposed to reduce the burden of disease in patients with bulky disease [Jacob *et al*. 1991; Schwartz *et al*. 1994; Vergote*et al*. 1998, 2000]. While the standard approach for treating patients with advanced EOC remains PDS followed by platinum-based chemotherapy, NACT-IDS is a treatment approach for patients with massively disseminated tumors [Schwartz, 2008, 2009; Fago-Olsen *et al*. 2014].

In recent years, NACT-IDS has gained credibility as a valid therapeutic strategy especially for patients with stage IV unresectable bulky tumors or poor general condition [Cannistra, 2004; Rauh-Hain*et al*.2012]. The latest retrospective studies verified the clinical significance of NACT-IDS. A Danish group compared the outcomes of NACT-IDS (*n* = 515) with PDS (*n* = 990). No difference in median OS was observed between PDS and NACT-IDS. However, patients without residual tumor had a better median OS when treated with PDS. In a multivariate analysis, NACT-IDS was associated with an increased risk of death after 2 years of follow up (HR 1.81, CI 1.39–2.35) [Fago-Olsen *et al.* 2014]. Based on these findings, NACT-IDS has become a primary treatment for patients with advanced EOC [Vergote*et al.* 2011b; Cornelis*et al.* 2012]. However, despite NACT being useful for patients in whom optimal debulking appears impossible, primary surgical cytoreduction should not be precluded by a lack of surgical skills and experience [Chi *et al.* 2012; Vergote*et al.* 2013].

The EORTC trial included quality of life as a secondary endpoint [Vergote*et al*. 2010]. Survival and QOL after NACT followed by surgery was similar to that after PDS followed by chemotherapy. However, institutions with good QOL compliance had a higher optimal debulking rate and better survival outcomes [Greimel*et al*. 2013]. Schwartz and colleagues reported that the NACT group had a poor PS and were significantly older compared with the PDS group in stage IIIC and IV cases; however, the length of hospital stay was significantly shorter in the IDS group [Schwartz *et al*. 1999]. These observations suggest that NACT plays an important role in maintaining QOL of patients with advanced EOC. Because advanced EOC is a disease that can rarely be cured, QOL should be evaluated as an endpoint in clinical trials of NACT.

Non-inferiority of NACT-IDS to PDS has been demonstrated in randomized controlled trials. However, there is still no evidence that NACT is superior to standard treatment. The biggest risk associated with use of NACT is that patients with significant side effects and refractory disease will lose the opportunity for initial surgery. Establishment of an optimal regimen is necessary in order to improve the outcome of NACT. Furthermore, the precise role of NACT in the management of advanced EOC has not yet been established. Therefore, PDS should be the mainstay of treatment whenever possible to protect patients from disease progression on NACT and losing the opportunity for initial surgery and primary surgical cytoreduction should not be precluded by a lack of surgical skills and experience [Chi *et al.* 2012; Vergote*et al.* 2013].

The intraoperative initial disease burden was measured with the use of “OR tumor index.” Patients with a score of 0 had neither carcinomatosis nor bulky upper abdominal disease. Women with a score of 1 had either carcinomatosis or bulky upper abdominal disease, and those with a score of 2 had both carcinomatosis and bulky upper abdominal disease [Tanner *et al.* 2013].

Debulking procedures included: hysterectomy, salpingooophorectomy, omentectomy with or without gastrointestinal surgery, lymphadenectomy and radical upper abdominal procedures, such as diaphragm peritonectomy/resection, splenectomy, distal pancreatectomy, liver resection, and cholecystectomy. As described by Aletti et al.,2007 a surgical complexity score (CS), which incorporates the number and complexity of surgical procedures performed, was assigned to all patients. A CS ≤3 was defined as low, CS 4–7 as intermediate, and CS ≥8 as high.

**AIM OF THE WORK**

To study the impact of primary debulking surgery (PDS) to minimal but gross residual disease (RD) in women with locally advanced epithelial ovarian cancer versus neoajuvant chemotherapy and interval debulking surgery and comparison of the following objectives:

* Locoregional recurrence.
* Distant metastasis.
* Disease free survival and overall survival.

**PATIETS AND METHODS**

* ***Study design***

Propsective observational cohort study.

* ***Study setting and location***

National Cancer Institute (NCI) - Cairo University (CU)

* All patients with locally advanced epithelial ovarian cancer attending the National Cancer Institute will be analyzed dating from September 2017 till the end of January 2019 with a minimum follow up of 18 months.
* ***Study population***

Patients with stage III epithelial ovarian cancerwill undergo either primary debulking surgery or neoadjuvant chemotherapy and interval debulking surgery.

* ***Study timing:***
* Recruitment time:from September 2017 till the end of January 2019.
* Follow up time: minimum follow up of 18 months.
* **Eligibility Criteria**
* **Inclusion criteria**
* Patients with locally advanced epithelial ovarian cancer who will undergo the previously mentioned management.
* **Exclusion criteria**
* Patients with disease of non-epithelial histology or borderline tumors.
* Patients with locally advanced epithelial ovarian cancer who managed outside NCI.

Data will be retrieved from the files of the Biostatistics and Cancer Epidemiology Department, Surgical Department portal system and Pathology Department.

**Data retrievedfrom the medical records:**

Age at presentation

Sex

Symptoms and signs

Age at diagnosis

Body mass index (BMI)

Serum albumin and CA-125

Pretreatment stage

Comorbid disease

Histologic grade

**Radiological data:**

Abdominal ultrasound (US)

Computed tomography (CT)

Magnetic resonance imaging (MRI)

Image guided biopsy

**Data retrieved from the operative notes:**

Details on the operative time

Procedures performed

Volume of RD

Ascites

Estimated blood loss (EBL)

**Final pathological evaluation**:

Tumor size

Tumor deposits

Lymph node metastases

Histological type

Tumor grade

**Postoperative complications as:**

Wound infection

 Fistula

 Sepsis

* **PFS and OS** will be the endpoints of our study. PFS will be defined as the time interval from the date of PDS to the date of disease progression, death. OS will be calculated from the date of PDS to the date of death and the minimum follow up period will be 18 months.The purpose of the exploration will be to evaluate tumor resectability to perform primary debulking surgery when optimal cytoreduction seemed feasible and to treat primary unresectable tumors with neoadjuvant chemotherapy.

This strategy will be explained to the patients, and informed consent will be obtained. Neoadjuvant chemotherapy will be administered when the multidisciplinary team considers that optimal cytoreduction is not feasible with standard surgery. Conversely, primary debulking will be performed when the MDT considers that optimal debulking could be achieved with standard surgery.

 Clinical response to chemotherapy will be evaluated on clinical examination, serum CA 125 level, and computed tomography (CT) scan. Patients then will be referred for a second surgical exploration when they present no signs of clinical progression during chemotherapy. The tumor response to neoadjuvant chemotherapy will be assessed at secondary surgery.

 Based on the reported RD, patients will be classified into 4 groups: Group 1 included patients left with NGR; Group 2 included those left with RD of 1–5mm; Group 3 included those left with RD of 6–10mm; and Group 4 included those left with RD N10 mm.. Their classification follows the modified Clavien-Dindo system, as published elsewhere[18].

**Sample size estimation:**

All patients with locally advanced epithelial ovarian cancer attending at National Cancer Institute, Cairo Universitydating from September 2017 till the end of January 2019 will be included in that trial.

**Statistical Methods:**

Data will be analyzed using SPSS win statistical package version 22. Numerical data will be expressed as mean and standard deviation (SD), median and interquartile range or range as appropriate. Qualitative data will be expressed as frequency and percentage. Chi-square (Fisher's exact) test will be used to examine the relation between qualitative variables as appropriate.

Survival analysis will be done using Kaplan-Meier method. Comparison between two survival curves will be done using log rank test, Multivariate analysis will be done by Cox regression model to test for independent prognostic effect of statistically significant variables on univariate level with calculating hazard ratio and its 95% confidence interval.

Correction of P value will be done using Benferroni adjustment to avoid hyperinflation of type 1 error resulting from multiple comparisons. p-value ≤0.05 will be considered significant and all test was 2 tailed.

**Institutional Review Board Approval:**

This protocol and any accompanying material provided to the subject (such as descriptions of the study used to obtain informed consent) will be submitted by the Institutional Review Board (IRB). Approval from the committee will be obtained prior to initiating the study.

*Benefits from the study are:*

To assess the impact of primary debulking surgery (PDS) to minimal but gross residual disease (RD) in women with stage III epithelial ovarian cancer versus whom underwent neoajuvant chemotherapy and interval debulking surgery.

**Protection of privacy and confidentiality of patients’ information:**

Data collection and presentation will be anonymous and both privacy and confidentiality will be protected to the maximal possible standards.

**Publication policy:**

Any active participant involved in that work will be included in any publications for that work.

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**هل الاستئصال الجراحى الاولى لأورام المبيض الظاهرة المتقدمة ذو فاعلية مثل العلاج الكيمائى ثم الاستئصال الجراحى بالمعهد القومى للاورام ،جامعة القاهرة**

بروتوكول رسالة توطئة للحصول على درجة الدكتوراة في جراحة الأورام

**السيد محمد شاكر السيد شعير**

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**د/هالة عزيز شكر الله**

أستاذ مأمراض الباطنة و العلاج الكيميائى

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