Gynecologic Oncology xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Minimally invasive versus standard laparotomic interval debulking surgery in ovarian neoplasm: A single-institution retrospective case-control study

S. Gueli Alletti [a,*], M. Petrillo [b,c], G. Vizzielli [a], C. Bottoni [a], F. Nardelli [c], B. Costantini [a], L. Quagliozzi [a], V. Gallotta [a], G. Scambia [a,c], A. Fagotti [c]

[a] "Policlinico A. Gemelli" Foundation, L.go "A. Gemelli" n°8 00168, Rome, Italy
[b] Division of Gynecologic Oncology, "ARNAS Civico" Hospital, P.zza "N. Leotta" 4, 90127 Palermo, Italy
[c] Catholic University of the Sacred Heart, L.go "F. Vito" 1, 00168 Rome, Italy

HIGHLIGHTS

- A new frontier for laparoscopy in the management of ovarian cancer patients
- Minimally invasive approach provides improved surgical outcomes.
- MI-IDS plays a promising role in natural history of AEOC patients.
- Shorter TTC and administration of Bevacizumab seem to improve PFS.
- MI-IDS determines a significantly improved QoL after surgery.

ARTICLE INFO

Article history:
Received 25 July 2016
Received in revised form 7 October 2016
Accepted 9 October 2016
Available online xxxx

Keywords:
Ovarian cancer
Interval debulking surgery
Laparoscopy
Minimally invasive

ABSTRACT

Objective. To further investigate the role of MIS comparing patients submitted to MI-IDS with a balanced population treated by standard laparotomy.

Methods. The investigational arm (Cases) includes 30 AEOC patients treated with MI-IDS. The Control arm included a consecutive series of 65 AEOC patients submitted to laparotomic IDS. Inclusion criteria were: age > 18 years, histologically proven EOC, clinical complete/partial response after NACT, and ECOG PS <2. Preoperative clinical data, perioperative and oncological outcomes were analyzed. General Well-Being Schedule (GWBS) was administered to evaluate quality of life before and after surgery.

Results. Both groups were well-balanced. A higher percentage of women among Cases received bevacizumab-containing NACT compared with Controls.
No statistical differences were registered in terms of surgical procedures and residual tumor.
A significantly longer median OT in Cases was counterbalanced by more favorable EBL and median length of stay and TTC. No statistically significant differences were registered in terms of postoperative complications.
Cases showed a 6 months longer PFS compared to Controls. However, in multivariate analysis only the administration of Bevacizumab and a shorter TTC were independently associated with a longer PFS.
Regarding QoL, no statistically significant differences were registered in Cases between pre- and postoperative GWBS score. Differently from Controls where this difference was statistically significant and a more intense distress were recorded.

Conclusions. Minimally invasive approach could represent an advantageous alternative surgical way to perform interval debulking surgery in this specific subset of patients, with no impact on PFS. Based on these findings a randomized clinical trial is now under evaluation in our Institution.

1. Introduction

Primary debulking surgery (PDS) followed by chemotherapy with paclitaxel/carboplatin is the cornerstone of treatment for advanced-stage epithelial ovarian cancer (AEOC). Residual tumor at

* Corresponding author at: Dept. Obstetrics and Gynecologic, "Policlinico A. Gemelli" Foundation, L.go A. Gemelli, 8, 00168 Rome, Italy.
E-mail address: gueliallettis@gmail.com (S. Gueli Alletti).

http://dx.doi.org/10.1016/j.ygyno.2016.10.017
0090-8258/

the end of surgery represents one of the most important prognostic factors [1].

Neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) is considered to be an alternative treatment in patients unable to undergo complete resection during PDS. Two randomized clinical trials have demonstrated that patients with optimal cytoreduction after neoadjuvant chemotherapy have approximately the same survival rate than patients optimally cytoreduced at primary debulking surgery [2,3].

In AEOC laparoscopy has been introduced into NCCN guidelines as a valid tool to identify patients deemed unresectable at primary surgery and to obtain a histological diagnosis avoiding an unnecessary exploratory laparotomy [1].

In the last decade, thanks to technological progresses, we have observed increasing indications for MIS in ovarian cancer [4]. Starting from an exclusively diagnostic and explorative role in AEOC patients [5], laparoscopy has been introduced in the surgical management of early stage ovarian cancer [6] and in NACT patients in order to identify non responders to submit to a second-line chemotherapy [7]. Moreover, MIS allows complex procedures to be performed at the level of the upper and lower abdomen, in case of selected patients with recurrent ovarian cancer [8].

More recently, MIS has been proposed as a possible tool for cytoreductive surgery in AEOC patients after NACT [9–11] with the objective of extending to them the benefits of such approach in terms of surgical impact and fast recovery.

On the basis of these pioneer experiences we and others suggested that Minimally invasive Interval Debulking Surgery (MI-IDS) could be considered safe and feasible in patients with complete clinical response.

The purpose of our study is to further investigate the role of MIS in this clinical setting comparing patients submitted to MI-IDS with a balanced population treated by standard laparotomy.

2. Material and methods

This is a retrospective case-control study, where the investigational arm (Cases) includes 30 patients with high-grade serous AEOC admitted at the Division of Gynecologic Oncology at the "Policlinico A. Gemelli" Foundation of Rome between April 2013 and August 2014, judged unsuitable for PDS at staging laparoscopy, and treated with NACT followed by MI-IDS. After IDS, all women received the same chemotherapy regimen administered preoperatively for a total of 6 cycles. Patients who received Bevacizumab containing NACT received also maintenance treatment until disease progression or for a maximum of 15 months.

The control arm included a consecutive series of 65 high-grade serous AEOC patients, admitted at the same Institutions between April 2010 and September 2014, selected at staging laparoscopy for NACT and treated with standard laparotomic IDS.

In both groups inclusion criteria were the following: age > 18 years, histologically proven EOC, clinical complete/partial response after NACT, and ECOG PS <2. Women with ASA III-IV and body mass index (BMI) >40 kg/m^2 were excluded. Clinical response was assessed according to GCIG and RECIST criteria [12,13]. Completeness of response according to 1 of the 2 criteria was sufficient to include the patient in the protocol. All patients were not selected on type or number of NACT cycles.

For all patients, preoperative data (type and number of cycles of NACT, pre/post-chemotherapy CA-125 serum levels, and computed tomography [CT] scan results) were collected. In addition, all surgical procedures started with S-LPS with the objective to assess surgical complexity on the basis of residual disease localization, if present.

Perioperative outcomes (operative time, estimated blood loss, conversion to laparotomy, surgical procedures, residual tumor size, ileus, hospital discharge, days needed to restart chemotherapy, and histological findings) were registered. Early postoperative complications were registered according to the Memorial Sloan Kettering Cancer Center grading system [14]. Data regarding prognosis, recurrence rate, pattern of recurrence, progression free survival were also analyzed.

In particular, for patients submitted to MI-IDS, these data were prospectively gathered in the context of the previously registered "MISSION trial" (NCT02324595).

All patients were also administered a psychometric test, the General Well-Being Schedule (GWBS), to evaluate quality of life before and after surgery [15].

2.1. Surgical procedures

A careful exploration of the peritoneal cavity was the first surgical step. A 10-mm, flexible-tip, HD 3-dimensional video-laparoscope (Olympus) was used to explore all peritoneal recesses.

In the Cases, either three 5-mm trocars were placed in standard position for laparoscopy, or standard surgical setting for robotic procedures da Vinci Xi platform (Intuitive Surgical) were used.

In the Controls a middle laparotomic xifo-pubic incision was performed.

In both groups, standard IDS consisted in total/radical hysterectomy, BSO, omentectomy, and pelvic or upper peritonectomy. Traditionally, we do not perform systematic pelvic and aortic lymphadenectomy, in absence of residual disease at this level, detectable at radiological imaging and/or macroscopically [16]. Additional abdominal procedures (e.g., anterior rectal resection) were performed if needed. In case of increased surgical complexity additional trocars were placed in the right or left subcostal spaces. Advanced multifunctional instruments were used to optimize advanced surgical procedures in terms of efficacy, safety, and operative time. At the end of surgery, residual tumor was registered.

2.2. Follow-up

Follow-up consisted of gynecological examination, abdominal and pelvic ultrasonography, CA-125 serum levels every 3 months, and chest and abdomen CT scan every 6 months for the first 2 years. In case of increased CA-125 serum levels and/or suspicious CT scan findings, a PET/CT scan was requested to confirm recurrence.

2.3. GWBS

The GWBS is a psychometric test to assess the state of general well-being of the patients [15]. The scale determines how the person feels about her inner state rather than the outer; the 6 dimensions investigated are: anxiety, depression, general health, positive well-being, self-control, and vitality. The 3 scores are: severe discomfort (range 0–60), moderate discomfort (range 61–72), and wellness (range 73–110). A psycho-oncologist administered the test to all women in the study.

In particular, the GWBS results were registered at the end of NACT, 4 weeks before IDS, as basal record and within 30 days after surgery with the aim to establish the real impact of different approaches.

2.4. Statistical analysis

To avoid imbalance between the two groups in terms of initial disease extension and clinical features, the controls were matched with the cases as closely as possible using Stata software version 11.0 (Stata Corp, College Station, TX). Furthermore, to maximize the power of the study, cases and controls were matched in a 1:2 ratio. Differences between cases and controls were analyzed using the Pearson Chi-square exact test and Kruskall-Wallis test, as appropriate. Regarding survival analysis, Progression-free survival (PFS) was defined as the time elapsed from initial diagnosis to relapse or last follow-up visit. Medians and life tables were computed using the product limit estimate by Kaplan–Meier method [17], and the log-rank test was used to assess the statistical significance [18]. Cox's regression model with stepwise

Please cite this article as: S. Gueli Alletti, et al., Minimally invasive versus standard laparotomic interval debulking surgery in ovarian neoplasm: A single-institution retrospective ..., Gynecol Oncol (2016), http://dx.doi.org/10.1016/j.ygyno.2016.10.017