Interval debulking in epithelial ovarian carcinomas: the past, present and the future

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Summary

Primary cytoreductive surgery followed by combination chemotherapy of paclitaxel and cisplatinum is the standard treatment for advanced staged epithelial ovarian cancers. Despite the maximal efforts to increase optimal cytoreductive success rates and related ultra-radical surgeries, five-year survival rates are still poor. Primary cytoreductive surgeries and their radicalities have been criticized since the early nineties. Interval debulking surgery (IDS) and neo-adjuvant chemotherapy (NAC) are the two suggested alternatives to the primary debulking approaches. In this article, the authors summarize and discuss the IDS approach with an associated literature review.

Key words: Interval debulking surgery; Interval laparotomy; Epithelial ovarian carcinoma.

Introduction

Epithelial ovarian carcinomas are the most lethal genital malignancies. About two-thirds of the patients present with advanced staged disease and five-year survival rates are between 15-30% in Stage III-IV disease [1]. Today, optimal cytoreductive surgery followed by a combination of platinum and taxane-based chemotherapy is the standard treatment of ovarian cancers. With the recent developments in the surgical treatment of ovarian cancers, survival rates have risen by 50% in some modern oncology clinics [2]. However, it is still far from being a satisfactory rise, especially when one thinks about the excess morbidity related to these treatments. Thus physicians have tried different treatments such as neoadjuvant chemotherapy and interval debulking surgery (IDS) as an alternative to the standard treatment with primary cytoreductive surgery and chemotherapy.

Criticisms of optimal cytoreduction

Optimal cytoreduction is suggested to be the unique prognostic factor for advanced staged ovarian cancer patients [3-5]. Each 10% increase in optimal cytoreduction was suggested to equal a 5.5% increase in the overall survival of these patients [6]. However, maximal cytoreductive surgeries have been criticized by some authors since the early nineties (Table 1). These objections were particularly more important in advanced stages: 1) Despite the maximal efforts, optimal cytoreduction rates are less in these patients compared to early staged patients; 2) Patients with suboptimal cytoreductive outcomes had even worse prognosis in advanced stages; 3) Median survival gain achieved by ultra-radical surgeries is less in advanced stages (5.8% gain if < 1 cm residual and 6.9% gain if microscopic residual is left); 4) To achieve optimal cytoreduction, much more radicalism and extensive surgeries should be performed which may be associated with higher morbidities (serious morbidity 8-68%) and higher mortalities (1-7%); 5) There is still not enough data about the economic burdens of these debulking surgeries; 6) None of the authors analyzed the patients' quality of life with these radical surgeries performed to achieve optimal cytoreduction [7, 8]. These objections have directed physicians toward newer therapeutic modalities.

Terminology

As a definition, interval debulking surgery (IDS) and neoadjuvant chemotherapy (NAC) are frequently misused intervariably [9-11]. Neither are the standard treatment in epithelial ovarian carcinomas. Both strategies need a pathological diagnosis before treatment can be started and neither can be used in patients with progressive diseases. Both methods use chemotherapy but optimal regimens and numbers of chemotherapy cycles are still unknown [9-14].

NAC and IDS are basically two different approaches used in ovarian cancers. NAC is frequently used in patients with poor performance status (massive ascites, comorbid diseases or excess tumor load) that renders optimal cytoreduction or extensive debulking surgery. Following the tissue diagnosis with biopsy or cytology, patients will receive three to six cycles of chemotherapy. Patients who have a partial or complete response will undergo primary debulking surgery. Therefore, in neoad-

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Table 1. — *General criticisms about cytoreductive surgeries*.

1. No prospective randomized study evaluating the effects.
2. High inter-observer variability in assessing the residual disease.
3. Different definitions for residual disease (gram, cm^3, cm).
4. A possible delay in initiating the chemotherapy.
5. High morbidity and possible high mortality.
6. Unknown competitive or cooperative effects of surgical experience and intrinsic tumor biology for optimal cytoreduction.
7. No randomized study comparing new chemotherapeutic agents and regimens with the cytoreductive surgeries.
8. Debated and unresolved effects on patients' quality of life.

juvant chemotherapy we use a primary preoperative chemotherapy [9-14].

Different from NAC, interval debulking surgery is performed on patients who were not optimally cytoreduced during primary debulking surgery. It is not a procedure performed for poor performance status that renders a debulking surgery. Patients undergo debulking surgery but can not achieve optimal cytoreductive success and receive three to six cycles of postoperative chemotherapy (not primary neoadjuvant chemotherapy). Following the chemotherapy, patients with a partial or complete response are reevaluated for a second surgery (IDS) to finally achieve optimal cytoreduction [9-14].

Interval debulking: the past

Unlike the numerous NAC trials, interval debulking surgery (IDS) was not frequently analyzed previously. There are three randomized prospective reports up to date.

Redman *et al*. were the first authors who evaluated IDS [14]. Between 1986 and 1994, 79 patients with an initial suboptimal cytoreductive surgery (> 2 cm residual disease) were prospectively evaluated. All the patients received three cycles of platinum-based chemotherapy postoperatively. Following the initial chemotherapy, patients were randomized to an interval laparotomy (n = 37) vs additional chemotherapy (n = 42). While 37 underwent interval debulking surgery followed by three additional cycles of chemotherapy, the remaining 42 patients directly received an additional three cycles of platinum-based chemotherapy without any interval surgery. IDS significantly increased the optimal cytoreduction rate (73% of patients who had IDS received optimal cytoreduction). It also increased the median survival (15 vs 12 months) and decreased the mortality (OR = 0.70; 95% CI = 0.44-1.33), however these differences were not statistically significant [15].

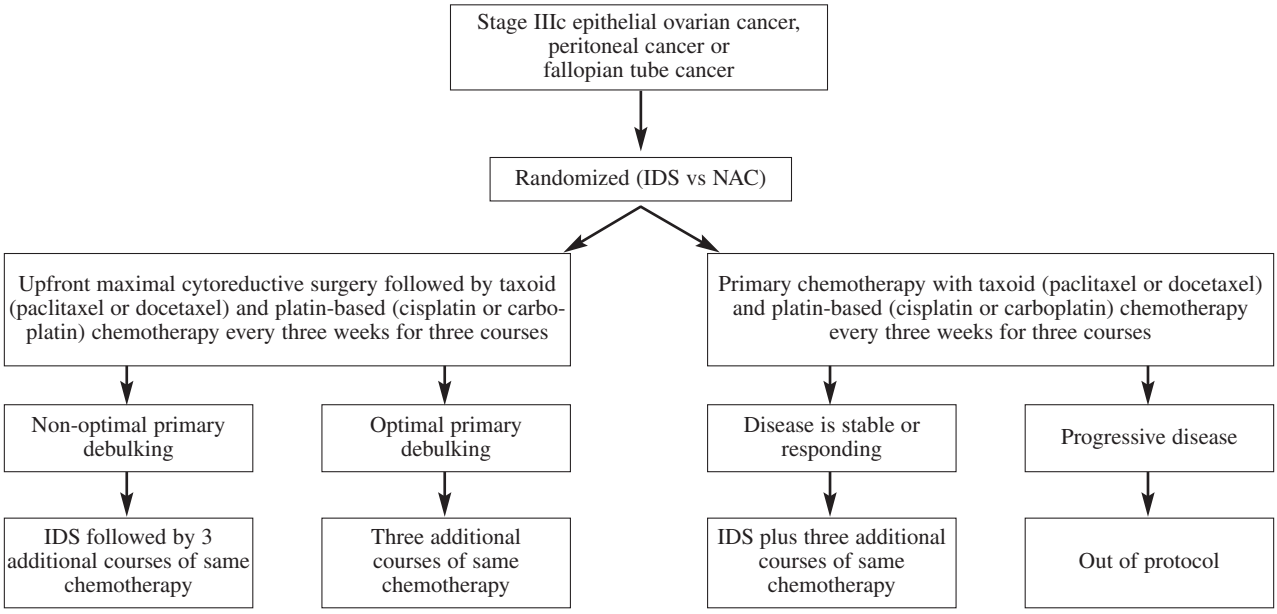
During 1987-1993, the European Organization for Research into Therapy for Cancer (EORTC), Gynecologic Cancer Cooperative Group (GCCG) conducted a prospective randomized study: EORTC/GCCG 55865 [15]. Two hundred and seventy-eight ovarian cancer patients with Stage IIB-IV disease with an initial suboptimal (> 1 cm residual disease) cytoreductive success received three cycles of cisplatin (75 mg/m^2) plus cyclophosphamide (750 mg/m^2). Following the initial debulking and three cycles of chemotherapy, patients were prospectively randomized. One hundred and forty patients underwent an interval laparotomy followed by three additional cycles of the same chemotherapy. Two-year overall survival (OS) and progression-free survival (PFS) were 56% and 38%, respectively. Median OS was 26 months and median PFS was 18 months. The remaining 138 patients received three additional cycles of the same chemotherapy without any interval debulking surgery. Two-year OS and PFS were 46% and 28%, and median OS and PFS were 20 and 13 months, respectively. These differences were statistically significant, favoring the IDS. Interval laparotomy approach increased PFS by five months, OS by six months and decreased the death risk due to disease by 33%. The authors also pointed out an important issue. Some patients had optimal debulking with the effect of three cycles of chemotherapy before the IDS (chemo-debulked). Patients who had optimal debulking before (chemo-debulked) or after the IDS had significantly higher survival rates compared to patients who remained suboptimally debulked after the IDS. Interval debulking surgery did not cause any additional morbidity or mortality for the patients and also did not cause any delay in the final treatment of patients. IDS was a significant factor on multivariate survival analysis ($p = 0.0012$).

However, further subgroup analyses of EORTC/GCCG 55865 produced some confusion in the minds of some [8]: 1) Survival of patients with > 1 cm residual disease after IDS was similar to the patients in the chemotherapy arm who did not undergo the IDS procedure (19.4 months vs 20 months, respectively); 2) Another debate was the better survival of chemo-debulked patients (< 1 cm before IDS) compared to the survival of patients who were optimally debulked after IDS (41 vs 26.6 months). Perhaps intrinsic tumor chemo-sensitivity may be more important for overall survival, but not for IDS which results in optimal debulking; 3) Second-look laparotomy results were similar in both arms. Complete pathological response was achieved in 37% of the IDS and in 33% of the chemotherapy arms; 4) Only 29% of the patients were optimally debulked at IDS. About 35% were preoperatively chemo-debulked and the remaining 36% of patients in the IDS arm could not achieve optimal debulking (failed IDS); 5) There were also questions related to the quality of life and the long term follow-up [17, 18].

In 1998, three years after the initial report, the authors reported their sixth year follow-up results [12]. Decrease in risk of death due to disease was still continuing with an absolute increase up to 60% (compared to 33% in the initial report). Interval debulking was still significant on multivariate survival analysis and the authors started to ask who could benefit from IDS surgery? However, they could not find any subgroup of epithelial ovarian cancer patients who had benefitted from IDS.

Six years later, at the 10th biennial International Gynecologic Cancer Society (IGCS) Meeting held in Edin-

Table 2. — *Clinical trial design of EORTC 55971.*



burgh in 2004, the authors announced their results after a ten-year follow-up (oral presentation). They still found IDS to be an important prognostic factor for both overall and progression-free survival (10-year OS was 13.8% vs 7.4%, $p < 0.0001$ and PFS was 9.6% vs 3.8%, $p < 0.0001$). Ten-year survival was 28.9% in chemo-debulked patients while it was 20.2% in successfully debulked IDS patients and 1.55% in unsuccessfully debulked IDS patients. Decrease in risk of death due to disease (40%) was still continuing despite an absolute decrease compared to the previous report (60%).

In the year 2002, Rose *et al*. reported the third randomized multi-center study held in the USA: GOG-152 [11]. They prospectively randomized 425 patients with FIGO Stage III disease and who had undergone suboptimal primary debulking surgery (> 1 cm residual disease) from 1994-2001. All the patients received three cycles of paclitaxel and cisplatinum combination chemotherapy after the initial suboptimal debulking surgery. Two hundred and sixteen patients were randomized to the surgery arm (interval debulking followed by a further 3 cycles of paclitaxel and cisplatinum). The median overall and progression free survivals were 32 and 10.5 months, respectively. The remaining 209 patients were randomized to the chemotherapy arm (only an additional 3 cycles of paclitaxel and cisplatinium without any interval debulking surgery). The median overall and progression-free survivals were 33 and 10.8 months, respectively. Comparison of both the overall and progression-free survivals could not differentiate any significant difference in either arm.

GOG-152 produced new questions and confusion in the minds. In contrast to the EORTC study with a 10-year follow-up, GOG-152 could not find any differences in the arms. These different results from the two large multicenter studies may be due to some subtle differences among the designs of the trials. All the participants in the GOG study were specially trained and experienced gynecologic oncologists. They probably used maximal effort for optimal debulking in the initial cytoreductive surgery before IDS. However, most of the EORTC trial participants were gynecologists or general surgeons. Therefore, patients may have had insufficient primary surgery before IDS in the EORTC trial. Another difference between the two trials was the different regimens used (paclitaxel vs cyclophosphamide). This may also explain the different results of these trials. Therefore, one may suggest an indefinite conclusion that is 'these two trials are totally incomparable'.

Interval debulking: the future

The two prospective randomized trials could not resolve the ongoing debate on IDS. Also, although NAC was more frequently analyzed in the previous literature compared to the interval debulking strategy, there were still many questions to be answered regarding NAC. Furthermore, there was no report comparing these two strategies in any randomized prospective manner. These unresolved issues forced the EORTC to design a new prospective randomized trial, EORTC 55971, which started to enroll patients in 1998. The trial has four arms (Table 2) and also includes a quality of life assessment. It not only evaluates the NAC and IDS similar to the previous reports but also directly compares the two strategies.

Conclusion (interval debulking: the present)

Interval debulking surgery is not a standardized treatment option yet. However it can be performed in a selected patient population. For a final conclusion we need to await the long-term results of EORTC 55971.

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