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Review

Primary versus interval debulking surgery in the management of ovarian cancer patients, current data summary

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Abstract

Objective: Optimal management of ovarian cancer patients have been investigated by several centers and have been discussed in a great number of published articles. Aim of this article is the review of current data regarding this lethal malignancy treatment. Moreover, we discuss the ongoing trials regarding primary or interval cytoreductive surgery after neoadjuvant chemotherapy. **Mechanism**: We reviewed the relevant literature regarding ovarian cancer treatment via primary debulking surgery (PDS) as well as neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS). **Findings in Brief**: Our findings suggest that Neoadjuvant chemotherapy (NACT) and interval debulking surgery (IDS) are alternative treatments for advanced-stage ovarian cancer patients where optimal debulking surgery is considered unfeasible, while some studies indicate that NACT/IDS offer similar oncological outcomes with fewer postoperative complications. The prediction of optimal debulking probability can be evaluated by CA-125 level $\geq$500 U/mL, performance status $\geq$2, suprarenal paraaortic or supradiaphragmatic nodes $>$1 cm, Porta hepatis disease, diffuse serosal bowel carcinomatosis, bowel mesenteric involvement or a PIV score $\geq$8 if a laparoscopy is performed. **Conclusions**: Regarding the management of advanced ovarian cancer patientswho receive neoadjuvant interval debulking surgery seems to be as efficacient as primary cytoreduction. The patients that are more eligible and could benefit from this treatment strategy should be specified through larger, double-blind randomized control trials.

Keywords: ovarian cancer; primary debulking surgery; neoadjuvant chemotherapy; interval debulking surgery; optimal cytoreduction

1. Introduction

Ovarian cancer is the gynecological malignancy with the highest mortality. In 2020 over 313,959 patients were diagnosed with ovarian cancer, almost 207,252 died from ovarian cancer, while in the United States and Japan, ovarian cancer accounts for 2.5% and 3.1% of cancer diagnoses, respectively, and is the ninth leading cause of cancer-related death. While the cure of patients with early-stage disease exceeds 90%, patients with metastatic disease have a 5-year survival rate of 25%–30% [1]. Regarding the management, optimal cytoreduction where the largest residual tumor nodule measures 1cm or less and the subsequent adjuvant platinum-based chemotherapy is the golden standard, although in advanced stage cases, neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) and additional platinum-based chemotherapy, has been shown to offer similar oncological and survival rates along with comparable mortality and complication ones. However, it has been highlighted that in both upfront and intermediate debulking surgery should target complete cytoreduction in order to achieve better survival rates [2]. Thus, NACT and IDS is recommended in cases when PDS is predicted unfeasible and therefore the resectability criteria regarding ovarian carcinomas are of extreme significance. Interestingly, although many studies have investigated which are the predictive factors of a complete cytoreduction, no guidelines have been formed regarding the clear indications of performing an IDS instead of a PDS [3]. Poor performance status, severe comorbidities along with radiologically depicted or laparoscopically visualised visceral metastases in liver, porta hepatis, mesentery root of the small bowel, lesser sac or diaphragma, suprarenal lymphadenopathy or significant levels of tumor markers CA-125 and HE4 have been used as prediction tools in order to assess the feasibility of an optimal debulking surgery [4]. We reviewed the studies which provoked much discussion and debate regarding the role of NACT plus secondary cytoreduction in comparison with primary debulking among advanced ovarian, fallopian tube and primary peritoneal cancer patients and we aimed to luminate the patients' selection criteria for each management strategy.

2. Primary debulking surgery vs. NACT followed by interval debulking

2.1 The EORTC-NCIC trial

The first trial studying the oncological outcomes of neoadjuvant chemotherapy followed by interval debulking surgery vs. primary debulking surgery followed by chemotherapy as a treatment option for patients with bulky stage IIIC or IV ovarian, fallopian-tube, or primary peritoneal carcinoma was released by Vergote *et al.* [5] in 2010. Similar results were reported regarding the survival rates in both arms, with a median progression-free survival of 12 months, and a median overall survival rate of 29 months

for PDS vs. 30 months for NACT/IDS accordingly (hazard ratio for death, 1.00; 90% CI, 0.85 to 1.16; $p = 0.01$ for noninferiority). However, the postoperative morbidity and mortality rate was higher in the PDS group [5].

2.2 The SCORPION trial

The SCORPION trial evaluated the progression free survival (PFS) and perioperative complications among 171 epithelial ovarian, fallopian tube, or primary peritoneal cancer patients with advanced disease (Stage III/IV). Patients initially underwent laparoscopy to evaluate the tumor load, and subsequently randomized either primary debulking surgery followed by adjuvant chemotherapy or NACT, following an initial laparoscopy. The PDS arm included 84 patients and achieved a complete resection (R0) rate of 47%, while at the 87 patients included in the NACT/IDS arm, complete resection (R0) reached 77% ($p = 0.001$), with a 90% optimal resection in both arms. In terms of survival, no superiority of either of the methods was proved, with the median progression-free survival reaching 15 and 14 months in PDS and IDS arm respectively while overall survival rate was 41 and 43 months. However, the trial demonstrated a statistically significant difference in the complication rate, reaching 25.9% in the PDS arm, including a death rate of 8.3%, compared with 7.6% in the NACT group ($p = 0.0001$), without any postsurgical deaths [6].

2.3 The Chemotherapy or Upfront Surgery (CHORUS) trial

Similarly, the CHORUS trial randomly compared the overall survival between stage III or IV ovarian cancer patients receiving either PDS followed by adjuvant chemotherapy or 3 cycles NACT followed by IDS and another 3 additional cycles of completion chemotherapy. The median overall survival was 22.6 months in the primary-surgery arm vs. 24.1 months in the primary chemotherapy arm. Additionally, the median progression-free survival was 12 months in both groups. However, the trial reached only 16% vs. 40% debulking rate in the PDS and NACT group respectively. Postoperative adverse events grade 3 or 4 were more common in the PDS group (60 [24%] of 252 women vs. 30 [14%] of 209, $p = 0.0007$, and similarly the postsurgical death rate was higher in the PDS group too (14 women [6%] vs. 1 woman [$<1\%$], $p = 0.001$) [7].

Hence, the aforementioned trials highlight the fact that optimal primary debulking surgery and neoadjuvant chemotherapy plus optimal interval debulking surgery have similar efficacy, but the complication rate in the first group is higher. Nevertheless, three meta-analyses comparing PDS with NACT and IDS regarding the oncological outcomes and the adverse effects of the two management options, presented controversial findings. On the one hand, Chiofalo *et al*. [8] systematically reviewed the literature and conducted a meta-analysis comparing the OS and PFS of the methods as well as the complication rate and the hospital stay. They indicated equivalence of the methods regarding survival but a decrease in postoperative morbidity following NACT/IDS [8]. Contrariwise, in a large meta-analysis by, Xiaofeng *et al*. [9] including sixteen trials and 57,450 patients, PDS was associated with improved survival in comparison with NACT/IDS, although NACT excels again in terms of less postoperative complications and better complete cytoreduction rates. Therefore, a consensus on which of the PDS or NACT/IDS could be the preferred approach in the management of advanced epithelial ovarian cancer (EOC) is crucial for the scientific community and the clinical practice.

2.4 The TRUST and SUNNY trials

In the setting of furthermore clarifying the optimal management approach of advanced stage ovarian, fallopian, and peritoneal cancer patients, two currently ongoing phase III randomized controlled multicenter trials aim to overcome the limitations of the previous EORTC55971 and CHORUS achieving higher rate of complete cytoreduction and a high standard quality of participating centers. More specifically the TRUST trial [10], including 772 patients with a IIB to IVB disease stage, assures the surgical quality setting inclusion criteria for the participating centers that encompass to at least 50% of no gross residual (NGR), a rate of $\geq$36 debulking-surgeries/year and a consent to be regularly evaluated by the TRUST quality committee. Similarly, the Asian SUNNY trial [11], evaluates the oncological efficacy of NACT followed by optimal IDS in 456 patients with stage IIIC or IV disease and guarantees a minimum of $\geq$50% complete resection rate in upfront surgery and only national cancer/designed ovarian cancer section/experienced in participating in ovarian cancer surgical trials centers are included. In both trials the patients in the PDS arm undergo upfront cytoreduction followed by 6 cycles of chemotherapy, whereas patients in the NACT/IDS arm undergo 3 cycles of neoadjuvant chemotherapy followed by interval debulking surgery and subsequently, 3 cycles of adjuvant chemotherapy. The primary endpoint of the studies is the overall survival, and the estimated completion date is expected in 2024 and 2023 respectively.

The most important prognostic factor regarding the survival of the advanced stage epithelial ovarian, fallopian, and peritoneal malignancies is tumor load of residual disease after maximal surgical cytoreduction. However, to this point, no accurate criteria have been formed in order to evaluate which patients are eligible for upfront surgery. In that setting, the approach of NACT/IDS is mainly selected for cases where a primary debulking is expected to be suboptimal. Here, we present a review of the up-to-date assessment tools that have been utilized in order to select the PDS or NACT/IDS candidates.

Historically, complete cytoreduction probability was evaluated using tumor markers such as CA-125 and HE4 and hematological parameters such as lymphocyte-

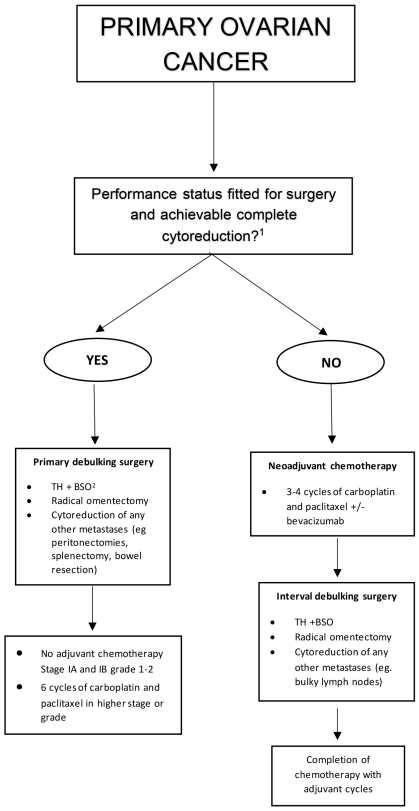

Fig. 1. Primary ovarian cancer treatment algorithm.

monocyte ratio (LMR), CA-125 levels over 500 U/mL usually indicating suboptimal debulking and increased LMR being associated with optimal surgery [4]. An interesting identification tool named Predictive Index Score was introduced by Bristow *et al.* [12]. The model assesses CT features of advanced ovarian cancer patients and correlates them with the surgical outcome. Peritoneal thickening, peritoneal implants (>/=2 cm), bowel mesentery involvement (>/=2 cm), suprarenal paraaortic lymph nodes (>/=1 cm), omental extension (spleen, stomach, or lesser sac), and pelvic sidewall involvement and/or hydroureter are poorly associated with optimal cytoreduction. More specifically, a preoperative PIS >/=4 is rarely observed in ovarian cancer patients with optimally resectable disease. Interestingly, although CT scans are the most common preoperative images among ovarian cancer patients, several recent studies have indicated that diffusion-weighted MRI (DW-MRI) and PET/CT techniques may be of higher diagnostic accuracy in metastases detection [4]. Additionally, some authors have used the combination of clinical factors and radiological images to predict optimal debulking surgery rates. Suidan *et al.* [13] in a prospective, non-randomized, multicenter trial of 350 stage III-IV epithelial ovarian cancer patients undergoing primary debulking. Clinical and radiological criteria were investigated and 11 were found to be predictive of a residual disease (RD). Analytically, (1) age ≥60 years, (2) CA-125 ≥600 U/mL, (3) ASA 3–4, (4) superior mesenteric artery root involvement, as well as detectable disease at the (5) splenic hilum/ligaments, (6) gastrohepatic ligament/porta hepatis, (7) gallbladder fossa/intersegmental fissure, (8) lesser sac lesions >1 cm, (9) suprarenal retroperitoneal lymph nodes, (10) small bowel adhesions/thickening and (11) ascites were the parameters that we statistically associated with suboptimal cytoreduction. In fact, all the parameters were summarized in a final score, which predicted incomplete resectability when calculated to be higher than 9 [13].

Table 1. Criteria of non-eligibility of complete primary cytoreduction.

Criteria of non eligibility of complete primary cytoreduction
• CA-125 ≥500 U/mL
• Performance status ≥2
• Suprarenal paraaortic lymph nodes >1 cm
• Supradiaphragmatic lymph nodes >1 cm
• Porta hepatis disease/metastases
• Diffuse serosal small and/or large bowel carcinomatosis
• Bowel mesenteric involvement
• If laparoscopy performed PIV score ≥8

In general, the NACT/IDS approach is typically selected for women with a poor performance status and significant medical comorbidities, or patients where the initial operation was performed by a non-gynecologic oncologist [14]. Finally, a large study presented by Fagotti *et al.* [15] established the role of initial laparoscopy as an adequate method of assessing optimal cytoreduction patients with advanced ovarian cancer. The patients included in the study underwent both laparoscopy and subsequently laparotomy and the tumor load were evaluated in order to predict suboptimal cytoreduction. More specifically, they introduced an evaluation tool named predictive index value (PIV) score to investigate the probability of optimal debulking. The items used as criteria and the corresponding scores in case of unresectability were the following: (1) peritoneal carcinomatosis (score 2), (2) diaphragmatic carcinomatosis (score 2), (3) mesenteric disease (score 2), (4) omental involvement (score 2), (5) bowel infiltration (score 2), (6) stomach infiltration (score 2), and (7) liver metastases (score 2). The total predictive index value (PIV) was obtained by adding up the individual items relative to all parameters.

Interestingly, a PIV of ≥8 was associated with suboptimal cytoreduction, since the probability of optimal debulking was calculated as 0, while the overall accuracy rate of laparoscopy predicting optimal cytoreduction probability was calculated between 77.3 and 100% [15]. Fig. 1 presents the primary ovarian cancer treatment algorithm. Table 1 summarizes the criteria of non-eligibility of a complete primary cytoreduction. Table 2 presents the studies comparing

Table 2. Oncological efficacy and safety of PDS vs. NACT/IDS.

Trial name (year)	Resection rate	Median PFS (months)	Median OS (months)	Complication rate
EORTC-NCIC (2010)	R0-1: 41.6% vs. 80.6%.	12 vs. 12 hazard ratio for progressive disease: 1.01 90% CI, 0.89 to 1.15	29 vs. 30 hazard ratio for death, 1.00; 90% CI, 0.85 to 1.16; $p = 0.01$ for noninferiority	Postoperative death: 2.5% vs. 0.7% Grade 3 or 4 hemorrhage: 7.4% vs. 4.1% Infection: 8.1% vs. 1.7% Venous complications: 2.6% vs. 0%
SCORPION (2020)	R0 rate: 47% vs. 77% ($p = 0.001$)	15 vs. 14 HR 1.05, 95% CI, 0.77 to 1.44, $p = 0.73$	41 vs. 43 HR 1.12, 95% CI, 0.76 to 1.65, $p = 0.56$	25.9% vs. 7.6%, $p = 0.0001$
CHORUS (2015)	R0: 16% vs. 40%	22.6 vs. 24.1	12 in both groups	24% vs. 14%, $p = 0.0007$ postsurgical death 6% vs. $<1\%$, $p = 0.001$
TRUST (2019) SUNNY (2020)			*ongoing*	

the oncological efficacy and safety of PDS vs. NACT/IDS.

3. Conclusions

The gold standard of management for ovarian cancer patients is optimal debulking surgery, although recent large trials investigating the optimal treatment for advanced stage disease have fuel a growing trend to apply NACT followed by IDS in cases where complete cytoreduction seems unfeasible. Our study suggests that NACT-IDS can achieve similar oncological outcomes with minimized postoperative complications. Therefore, it is of great significance to evaluate the tumor load resectability in order to identify the eligible patients for primary cytoreduction. So far, various methods have been proposed to predict optimal cytoreduction probability, and they encompass hematologic parameters and tumor markers such as lymphocyte-monocyte ratio and CA-125 and HE4 levels respectively, radiological images as well as a combination of the two aforementioned parameters. Moreover, diagnostic laparoscopy is lately a very reliable method to optimally select patients eligible for primary debulking surgery. Large-scale randomized clinical trials of laparoscopic evaluation using the scoring system highlighted that this tool may be particularly useful. Therefore, an effort should be made to select patients with optimal cytoreduction prognoses using multiple methods, such as serum biomarkers, imaging studies, and diagnostic laparoscopy, and having discussions with multidisciplinary team to yield more results from large clinical trials.

Author contributions

VP—data collection, data analysis, manuscript writing; AF—data collection, data analysis, manuscript writing; CI—consultation, protocol development. All authors have been personally and actively involved in substantive work leading to the manuscript, and will hold themselves jointly and individually responsible for its content.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. CI is serving as one of the Editorial Board members/Guest editors of this journal. AF, VP is serving as one of the Guest editors of this journal. We declare that CI, AF, VP had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Giuseppe Ricci.

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