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REVIEW

Role of surgery and hyperthermic intraperitoneal chemotherapy in ovarian cancer☆

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Ovarian cancer is one of the deadliest gynaecological malignancies and tends to be diagnosed at an advanced stage. Similar to many malignancies, surgery plays a critical role in many aspects of ovarian cancer management. Hyperthermic intraperitoneal chemotherapy (HIPEC) involves the induction of hyperthermia and delivery of intraperitoneal chemotherapy directly into the peritoneal cavity. Combined with cytoreductive surgery, HIPEC is an emerging treatment modality for ovarian cancer. Ovarian cancer survival outcomes can be improved by treatment with surgery and HIPEC in selected patients. Thus, this study aimed to review the current role of surgery and HIPEC in epithelial ovarian cancer. Evidence from the monumental and recent literature will be introduced.

Key words: ovarian cancer, cytoreduction, surgery, HIPEC, prognosis, survival

INTRODUCTION

Ovarian cancer, one of the deadliest gynaecological malignancies, is a global burden. In 2020, 313 959 new ovarian cancer cases and 207 252 deaths from ovarian cancer were reported, ranking eighth in both incidence and mortality among all types of cancers affecting women.[1] The absence of cancer-specific symptoms and effective screening tools resulted in the diagnosis of ovarian cancer at an advanced stage with high disease recurrence and mortality rates.[2] Histologically, the most common type of ovarian cancer is epithelial ovarian cancer (EOC), which accounts for >90% of all cases.[3] The current standard treatment of EOC includes cytoreductive surgery (CRS) followed by taxane- and platinum-based chemotherapy.

Despite the recent advances in chemotherapeutic agents, targeted therapy, and immunotherapy, surgery remains the mainstay of treatment of several malignancies. In ovarian cancer, surgery plays a critical role in many aspects of management, from the staging of initial disease to cytoreduction of metastatic or recurrent disease.[4] Over the past 50 years, advances in CRS and chemotherapy have led to the improvements in the 5-year survival of patients with EOC.

Hyperthermic intraperitoneal (i.p.) chemotherapy (HIPEC) involves the induction of hyperthermia and delivery of i.p. chemotherapy directly into the peritoneal cavity in patients with peritoneal spread of certain malignancies such as gastric cancer, appendiceal cancer, colorectal cancer, and mesothelioma.[5] HIPEC allows the delivery of a high concentration of chemotherapy in the peritoneal cavity and improves chemotherapeutic agent absorption and susceptibility of cancer cells. In EOC, CRS followed by HIPEC appears to be promising, as a Dutch, multicenter, phase III trial showed improvement of recurrence and mortality rates after adding HIPEC to interval CRS in patients who received neoadjuvant chemotherapy (NACT) as treatment of International Federation of Gynecology and Obstetrics (FIGO) stage III EOC.[6] However, there are several issues to be solved regarding the use of HIPEC, such as the expansion of disease settings, standardisation of HIPEC methods, and toxicity.

Ovarian cancer survival outcomes can be improved by treatment with surgery and HIPEC in selected patients. Thus, this short review aimed to examine the role of surgery and HIPEC in EOC, especially in terms of improving the prognosis. A literature review was conducted to determine the impact of CRS and HIPEC on the survival outcomes of patients with EOC. We prioritised phase III randomised controlled trials (RCTs). We also searched prospective and retrospective observational studies, real-world experience studies, and ongoing clinical trials investigating this issue.

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ROLE OF SURGERY IN OVARIAN CANCER

Primary CRS in newly diagnosed ovarian cancer

Ovarian cancer tends to be diagnosed at an advanced stage. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results registries, >60% of patients with EOC are diagnosed with FIGO stage III-IV.[7] In this setting, primary CRS followed by taxane- and platinum-based combination chemotherapy is a well-established management strategy. The objective of surgery should be complete removal of macroscopic disease, as complete cytoreduction is one of the most important prognostic factors of survival.[8]

In 1998, Eisenkop et al.[9] conducted primary CRS in 163 consecutive patients with FIGO stage IIIC-IV EOC with the intention of excising or ablating all visible disease. In their prospective cohort, complete cytoreduction was achieved in 85.3% of patients and was associated with better overall survival (OS) than residual disease ≤1.0 cm.

In 2005, Chi et al.[10] reported the survival outcomes of 465 patients with FIGO stage IIIC EOC according to the residual tumour status after primary CRS. Patients who had no gross residual tumour showed significantly better OS than those with gross residual tumour.

In 2007, a retrospective study of 1895 patients with FIGO stage III EOC, collected from six Gynecologic Oncology Group (GOG) studies (111, 114, 132, 152, 158, and 172), reported survival outcomes according to residual disease status after primary CRS.[11] Patients with microscopic residual disease showed significantly better progression-free survival (PFS) than those with 0.1-1.0 cm and >1.0 cm residual disease (median, 33.0 versus 16.8 versus 14.1 months; $P < 0.001$). Patients with microscopic residual disease also showed the best OS (median, 71.9 versus 42.4 versus 35.0 months; $P < 0.001$).

The prognostic importance of complete cytoreduction was also confirmed by du Bois et al.[12] in 2009. In their exploratory analysis of 3126 patients with FIGO stage IIB-IV EOC, collected from three randomised trials from the Arbeitsgemeinschaft Gynäkologische Onkologie Ovarian Cancer Study Group (AGO-OVAR; 3, 5, and 7), complete cytoreduction after primary CRS was associated with significantly better PFS and OS than 0.1-1.0 cm or >1.0 cm residual tumours. Thus, the goal of primary CRS should be complete resection and removal of all macroscopic disease.

In real-world clinical practice, the complete cytoreduction rate of EOC patients is influenced by several factors, such as the surgical capacity of gynaecologic oncologists or surgeons and the volume of hospital or centre. These factors should also be considered in the management of EOC because complete cytoreduction is directly associated with improved survival outcomes.

According to a previous meta-analysis study which investigated the effect of specialised care for ovarian cancer patients, CRS was carried out more adequately by gynaecologic oncologists. When CRS was conducted by gynaecologic oncologists, compared with general gynaecologists, both optimal debulking [residual tumour <2 cm; pooled relative risk, 1.4; 95% confidence interval (CI), 1.2-1.5] and complete cytoreduction (pooled relative risk, 2.3; 95% CI, 1.5-3.5) were more commonly achieved. Moreover, the OS significantly improved when patients were treated in a specialised hospital. This meta-analysis study showed that the outcome of ovarian cancer is better when treatment is provided by a gynaecologic oncologist or in a specialised hospital.[13]

In the literature, treatment carried out at high-volume hospitals (HVHs) was associated with improved OS in patients with EOC.[14-16] Bristow et al.[15] conducted a retrospective study including 11 865 consecutive patients diagnosed with FIGO stage IIIC-IV EOC between 1996 and 2006 from the California Cancer Registry. Patients were classified according to the combination of the following care categories: HVH: ≥20 cases/year, low-volume hospital (LVH), high-volume physician (HVP: ≥10 cases/year), or low-volume physicians (LVP). Multivariate analysis revealed that an LVH/LVP combination, rather than an HVH/HVP combination, was an independent poor prognostic factor for OS [hazard ratio (HR), 1.31; 95% CI, 1.16-1.49]. This study implied that treatment at high-volume centres by high-volume surgeons is associated with improved survival. Furthermore, access to high-volume ovarian cancer providers is limited to patients with a low socioeconomic status.[15] In another retrospective study, Bristow et al.[16] suggested that high-volume centres are more likely to provide guideline adherence care for EOC patients.

Meanwhile, the surgical outcomes of advanced ovarian cancer can be improved by systematic optimisation. For example, a German research team implemented a structured quality management program in 2001. The key features of a quality management program were the formation and education of dedicated surgical teams, interdisciplinary preoperative and intraoperative consultation, complication management, and quality conferences, including assessment and benchmarking of morbidity and outcome. Subsequently, patients with newly diagnosed FIGO stage IIB-IV EOC showed significant improvement in complete resection rate (33%-62%) and median OS (26-45 months).[17]

Thus, adequate and sufficient education or training for gynaecologic oncologists and surgeons should be implemented. In this aspect, we believe that the dissemination of standardised operation records is the first step in quality control of surgical treatment. The Guidelines and Assurance Quality Committee of the European Society of Gynecologic Oncology (ESGO) has formed and now provides the Ovarian Cancer Operative Report form.[18] We can record the surgical approach and findings, surgical procedures, and residual disease systemically using this form. Such standardised records will facilitate quality assessment and collaborative works across the borders.

Once surgical capacity is fulfilled by the right gynaecologic oncologists and other surgeons at the right centre, the next step is to select patients suitable for primary CRS. To ascertain whether patients are fit for extensive CRS, we should evaluate the individuals' nutritional status, performance status, and comorbid conditions. To assess the

extent of disease and resectability, a diagnostic workup consisting of computed tomography (CT) scans or positron emission tomography (PET)-CT should be conducted. Some researchers have reported the clinical utility and accuracy of whole-body diffusion-weighted magnetic resonance imaging (MRI) for the assessment of metastatic sites and their resectability.[19] Rizzo et al.[19] reported that whole-body diffusion-weighted MRI was significantly better than CT in identifying the involvement of the mesentery, para-aortic lymph nodes, pelvis, large bowel, and sigmoid-rectum.

When the results of preoperative imaging are ambiguous or uncertain, diagnostic laparoscopy can be used to assess the sites of disease in patients with advanced ovarian cancer. Diagnostic laparoscopy is a useful tool for assessing intraperitoneal tumour burden and the possibility of undergoing optimal CRS.[20] Previously, Fagotti et al.[21] suggested a laparoscopy-based scoring system. In addition, diagnostic laparoscopy provides a pathologic diagnosis.[22] If the patient has acceptable operative morbidity and resection of all macroscopic disease is feasible based on preoperative evaluation, upfront or primary CRS followed by taxane- and platinum-based combination chemotherapy is the current standard of care.[23]

After CRS, postoperative recovery and initiation of chemotherapy without delay are essential. According to a post-trial *ad hoc* analysis of the GOG-218 study, a prolonged time interval between surgery and adjuvant chemotherapy had a negative impact on patients' OS.[24] In detail, patients with stage IV EOC with postoperative microscopic residual disease had an increased risk of death when the time from surgery to initiation of chemotherapy exceeded 25 days (HR, 3.44; 95% CI, 1.68-7.03). Meanwhile, ancillary analysis results of the prospective OVCAD study reported that delayed initiation of chemotherapy (>28 days) in patients with stage III-IV EOC with postoperative residual disease was associated with worse OS (HR, 2.24; 95% CI, 1.08-4.66; $P = 0.031$).[25] Therefore, surgical candidates and the extent of surgery must be carefully selected, and postoperative complications must be assessed and managed promptly to avoid delays in chemotherapy.

NACT followed by interval CRS

In general, patients with the following conditions are regarded as not suitable for primary CRS: (i) diffuse deep infiltration of the root of the small bowel mesentery; (ii) carcinomatosis of the small bowel involving large parts that resection would lead to a short bowel syndrome (remaining bowel <1.5 m); (iii) diffuse involvement or deep infiltration of the stomach, duodenum, or head or middle part of the pancreas; (iv) involvement of the celiac trunk, hepatic arteries, or left gastric artery; (v) central or multisegmental parenchymal liver metastases; (vi) multiple parenchymal lung metastases; (vii) nonresectable lymph nodes; and (viii) brain metastases.[23] For such patients and those with poor nutritional and/or performance status and severe comorbidities, NACT may be considered an alternative treatment strategy. However, it is difficult to determine whether primary CRS and NACT should be carried out in individuals with advanced ovarian cancer, and several factors must be checked in a balanced manner (Figure 1). Individual tumour biology, perioperative risks, tumour resectability, and surgical complexity should be considered collectively.[26] Some researchers have suggested an algorithm that incorporates diagnostic laparoscopy. For example, Eoh et al.[27] presented consecutive steps of carrying out imaging, frailty assessment, and diagnostic laparoscopy. Such algorithms may lead to a decrease in the risk of futile surgery and an increase in the complete cytoreduction rate.

Two monumental phase III RCTs, the EORTC 55971[28] and the CHORUS,[29] showed similar PFS and OS between NACT followed by the interval CRS arm and the upfront CRS arm in patients with advanced EOC. In a pooled analysis of the two RCTs, patients with stage IV disease who underwent NACT showed significantly better PFS (median, 10.6 versus 9.7 months; HR, 0.77; 95% CI, 0.59-1.00; $P = 0.049$) and OS (median, 24.3 versus 21.2 months; HR, 0.76; 95% CI, 0.58-1.00; $P = 0.048$) than those who underwent upfront CRS.[30]

Another phase III RCT, the SCORPION trial, included 171 patients with stage IIIC-IV EOC who had high tumour load assessed by laparoscopy. In this trial, similar PFS and OS were observed between the NACT followed by interval CRS and upfront CRS arms.[31] Nevertheless, perioperative moderate-to-severe morbidity and quality-of-life scores were more favourable in the NACT than in the upfront CRS arm.[32]

In a Japanese phase III RCT including 301 patients with FIGO stage III-IV EOC, the NACT arm underwent less invasive surgical treatment, such as a lower frequency of abdominal organ resection or distant metastases resection, compared with the upfront CRS arm.[33] The primary endpoint of this trial was OS; compared with upfront CRS, the preplanned non-inferiority HR margin for NACT was 1.161. However, this trial failed to confirm the non-inferiority of NACT,[34] in contrast to the EORTC 55971 and CHORUS trials. In addition to the differences in study designs and treatment protocols, such inconsistent results might be due to the following reasons. First, the upfront CRS arm of the Japanese trial had a higher suboptimal CRS rate (residual tumour ≥1 cm, 62.6%) and more frequently received subsequent interval CRS (49/147, 33.3%), suggesting that this arm may benefit from interval CRS. Second, the sample size was smaller and deaths in the Japanese trial were fewer than those in previous trials. Therefore, caution is required when interpreting the results of the Japanese study.

As mentioned above, NACT is a valuable treatment option for patients with stage IIIC-IV EOC, particularly in those with high tumour burden at presentation or poor performance status. However, there are some controversies regarding the EORTC 55971 and CHORUS trials. Considering that complete removal of the tumour, which is the most significant prognostic factor in advanced EOC, is well known and widely accepted, the complete cytoreduction rate of patients who underwent upfront CRS was relatively low in both trials (20.3% and 16.7%, respectively). Kang[35] pointed

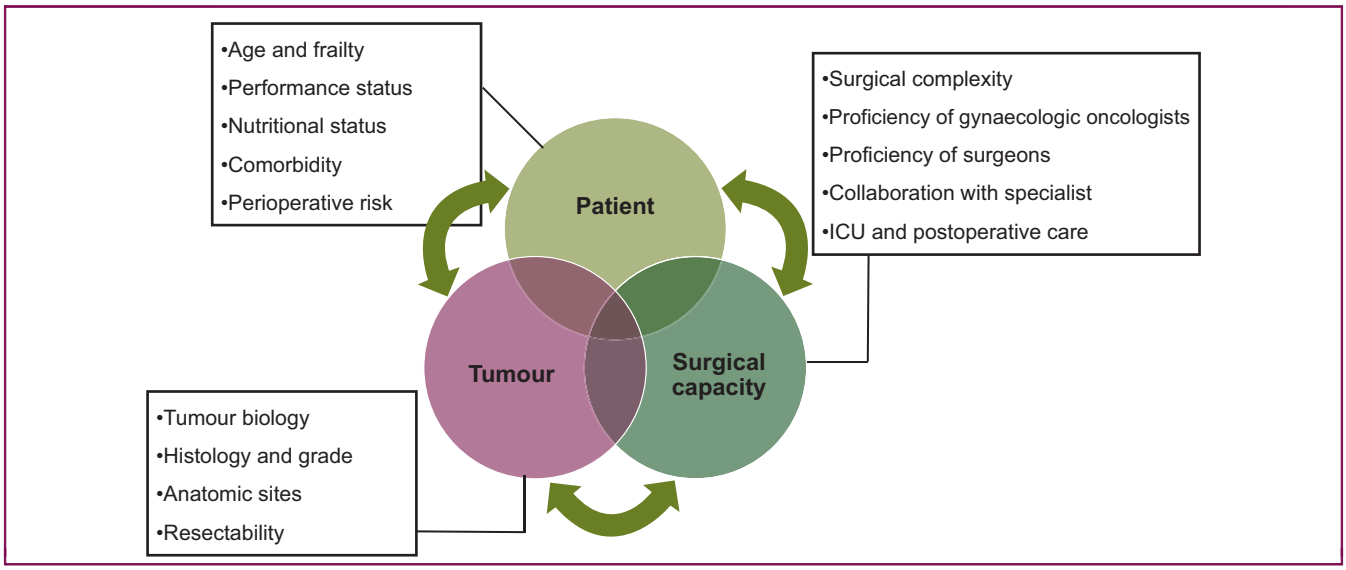

Figure 1. Factors should be considered in determining primary treatment strategy for newly diagnosed ovarian cancer.
ICU, intensive care unit.

out that both trials have similar weaknesses, which is the low quality of surgical care. For example, of all patients in the CHORUS trial's upfront CRS arm, 80% did not undergo upper abdominal surgeries, and the median operative time was only 120 min. The wide use of NACT might neglect the maximal surgical efforts of gynaecologic oncologists or improvement of competent surgical skills.[36]

Currently, there are two ongoing phase III RCTs, the TRUST from the ENGOT and AGO-OVAR groups[37] and the SUNNY from the Shanghai, Korean, and Japanese GOGs.[38] Of the two trials, the TRUST trial was designed based on the study hypothesis that upfront CRS is superior to NACT followed by interval CRS in terms of OS in patients with resectable FIGO stage IIIB-IV EOC. Uniquely, the TRUST trial adopted a qualification process for participating centres. To guarantee surgical quality, participating centres should meet the specific quality assurance criteria, such as $\geq$50% complete resection rate in upfront surgery and $\geq$36 debulking surgeries per year.[37] Both ongoing studies may show a survival benefit from upfront CRS in selected patients.

Interestingly, in real-world clinical practice, not all advanced EOC patients with NACT are able to undergo interval CRS. According to a retrospective study by the Memorial Sloan Kettering Cancer Center (MSKCC) group, of 224 patients with newly diagnosed EOC who received NACT, 62 (27.7%) did not undergo interval CRS. The non-surgical group was older, had more comorbidities, and had a lower performance status. The reasons for not receiving surgery were as follows: (i) inadequate response to NACT (39%), (ii) presence of comorbidities (24%), (iii) patient refusal (16%), (iv) death during NACT (15%), and (v) lost to follow-up (6%).[39] The study results suggest that more studies are needed to develop optimal therapies to maximise outcomes in this high-risk, elderly population. It should be noted, however, that the study population was highly selected; therefore, the study results should be interpreted with caution.

Some patients develop progressive disease (PD) during or after NACT, and the optimal treatment strategy for such patients is still unknown. In a two-institutional retrospective study conducted in Korea, patients who underwent CRS despite PD after NACT showed better OS than those who underwent salvage second-line chemotherapy (median, 19.4 versus 7.9 months; $P = 0.011$). However, the sample size was too small to conduct further analyses ($n = 36$). The study findings suggest that CRS may result in a survival benefit even in patients who developed PD after NACT.

Secondary CRS in recurrent ovarian cancer

For platinum-sensitive recurrent EOC, secondary CRS was conducted in selected patients. However, the choice of patients who will benefit from secondary CRS remains controversial. As in newly diagnosed EOC, the goal of secondary CRS is complete resection, as residual disease is associated with survival outcomes.

The MSKCC group reported that longer disease-free intervals, fewer recurrence sites, and $\leq$0.5 cm residual disease after secondary CRS are favourable prognostic factors.[40] Simultaneously, the AGO-OVAR group reported significantly better OS in patients who achieved complete cytoreduction after receiving secondary CRS than in those who had residual disease after surgery.[41] This study suggested the presence of all three factors: (i) no residual disease at primary surgery, (ii) good performance status [Eastern Cooperative Oncology Group (ECOG) 0], and (iii) no ascites, as a predictor of achieving complete cytoreduction at the time of secondary CRS. The AGO score was prospectively validated in the DESKTOP II trial.[42] Both the MSKCC and AGO-OVAR criteria helped identify patients who are suitable for secondary CRS. Figure 2 presents the nomograms constructed by Bogani et al.[43] to calculate the probability of complete cytoreduction based on each criterion for clinical utility.

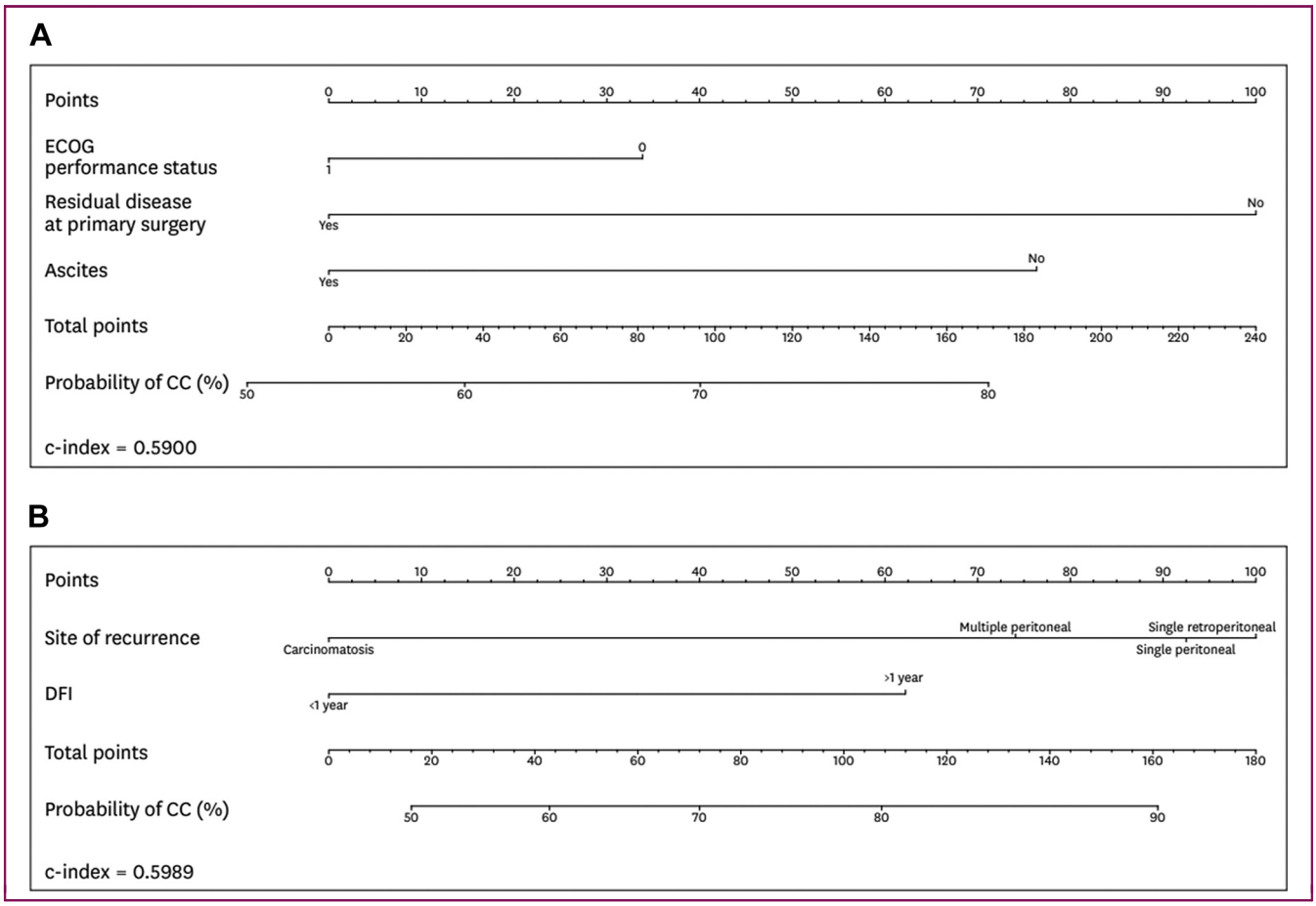

Figure 2. Nomograms displaying the probability of complete cytoreduction.
(A) Based on the Arbeitsgemeinschaft Gynäkologische Onkologie Ovarian Cancer Study Group (AGO-OVAR) criteria; (B) Based on the Memorial Sloan Kettering Cancer Center (MSKCC) criteria. Adapted with permission from Bogani et al.[43]
CC, complete cytoreduction; DFI, disease-free survival; ECOG, Eastern Cooperative Oncology Group.

Currently, another scoring system, the international model (iMODEL), is also available for predicting the feasibility of complete resection by secondary CRS.[44] The iMODEL consists of six factors: (i) FIGO stage (I-II versus III-IV), (ii) results of primary surgery (no residual versus residual), (iii) platinum-free interval ($\geq$16 versus $<$16 months), (iv) ECOG performance status (0-1 versus 2-3), (v) serum CA-125 levels at recurrence ($\leq$105 versus $>$105 IU/ml), and (vi) ascites (absent versus present). Each factor is scored between 0 and 3, and the total score is obtained. Validated externally, an iMODEL score $\leq$4.7 indicates a potentially complete resection.[44]

To date, three phase III RCTs from three different groups have validated the survival outcomes from secondary CRS in patients with platinum-sensitive, recurrent EOC. First, the GOG-213 trial randomly assigned 485 patients who had investigator-determined resectable disease (to no macroscopic residual disease) into the secondary CRS arm and chemotherapy alone arm.[45] Complete cytoreduction was achieved in 67% of patients in the surgery arm. In this trial, the use of adjuvant chemotherapy and bevacizumab was at the discretion of the investigator. Bevacizumab was administered to 84% of the patients and was equally distributed to the surgery and chemotherapy alone groups. As regards the primary endpoint, the median OS of the surgery and chemotherapy alone groups were 50.6 and 64.7 months, respectively; however, no significance was found in the HR for death (surgery versus no surgery, 1.29; 95% CI, 0.97-1.72; $P = 0.08$). The HR for disease progression or death (surgery versus no surgery) was 0.82 (95% CI, 0.66-1.01) and the PFS was similar between the two groups (median, 18.9 versus 16.2 months).

Second, the AGO DESKTOP III trial randomly assigned 408 AGO score-positive patients into the secondary CRS arm and chemotherapy alone arm.[46] Complete cytoreduction was achieved in 74.2% of the patients. OS, the primary endpoint, was significantly longer in the surgery group than in the chemotherapy alone group (median, 53.7 versus 46.0 months; HR, 0.75; 95% CI, 0.58-0.96; $P = 0.02$). The surgery group also showed significantly improved PFS compared with the chemotherapy alone group (median, 18.4 versus 14.0 months; HR, 0.66; 95% CI, 0.54-0.82; $P < 0.001$). In the surgery group, patients who achieved complete cytoreduction had much better OS than those with residual disease (median, 61.9 versus 28.8 months; HR, 0.40; 95% CI, 0.28-0.59; $P < 0.001$). The complete cytoreduction subgroup had an OS benefit of 15.9 months compared with the chemotherapy alone group (median, 61.9 versus 46.0

months; HR, 0.57; 95% CI, 0.43-0.76; $P < 0.001$). This was the first RCT to demonstrate the survival benefit of complete cytoreduction in patients with recurrent EOC.

Recently, the results of the SOC1/SGOG-OV2, another phase III RCT on secondary CRS, have also been reported.[47] This trial had a similar study design to the DESKTOP III trial, but used the iMODEL score combined with PET-CT imaging instead of the AGO score.[47] Although both GOG-213 and AGO DESKTOP III trials set OS as the primary endpoint, the SOC1/SGOG-OV2 trial set PFS and OS as co-primary endpoints. In total, 357 patients were enrolled: those who had an iMODEL score $\leq$4.7; or those who had an iMODEL score $>$4.7 with a serum CA-125 level $>$105 IU/ml but the principal investigators confirmed that the disease was resectable by PET-CT. Complete cytoreduction was achieved in 72.5% of the patients. The surgery group showed significantly better PFS than the chemotherapy alone group (median, 17.4 versus 11.9 months; HR, 0.58; 95% CI, 0.45-0.74; $P < 0.001$). Although the OS data are immature, the prespecified interim analysis of OS revealed no significant difference between the surgery group and chemotherapy alone group (median, 58.1 versus 53.9 months; HR, 0.82; 95% CI, 0.57-1.19).

These three RCTs showed differences in patient selection methods and complete cytoreduction rate. In terms of bevacizumab maintenance therapy, the proportion of patients receiving bevacizumab also differed among the studies: 84%, 23%, and 1% for the GOG-213, AGO DESKTOP III, and SOC1/SGOG-OV2 trials, respectively. In addition, the competence of the secondary CRS from each centre is an important issue. Therefore, attention should be paid when interpreting the study results and applying them to each institution. There remain unanswered questions regarding secondary CRS. First, the development of better patient selection criteria is necessary to avoid or minimise futile secondary CRS. Second, the survival benefit from secondary CRS might differ according to the tumour biology (e.g. histological subtype of EOC). Third, we were unable to determine which maintenance strategies should be administered after surgery [e.g. bevacizumab, poly(ADP-ribose) polymerase (PARP) inhibitors, immune checkpoint inhibitors, or a combination of these therapies]. Thus, further prospective studies are warranted to investigate the optimal maintenance therapy after secondary CRS according to the residual disease and the individual patients' *BRCA1/2* mutation or homologous recombination deficiency status.

ROLE OF HIPEC IN OVARIAN CANCER

HIPEC after CRS has been extensively studied in patients with peritoneal carcinomatosis from various malignancies, including colorectal and gastric cancers.[48,49] Compared with conventional i.p. chemotherapy, HIPEC has several advantages, including synergistic effects. Hyperthermia has direct cytotoxic effects on tumour cells and increases the penetration of chemotherapy and drug concentration at the peritoneal surface. HIPEC is conducted in a single session; therefore, there are no potential catheter-related complications.[50]

Regarding EOC, the literature on HIPEC is limited. Most studies were conducted at a single institution with a small sample size. Detailed methods of HIPEC, regimens, and dosages of chemotherapeutic agents (e.g. cisplatin or paclitaxel), and disease setting (e.g. newly diagnosed or recurrent EOC) were different among the previous studies, which is also observed in ongoing clinical trials.[51] Thus, when, how, and on whom HIPEC should be carried out remains a significant issue.

At the 2017 ASCO annual meeting, Lim et al.[52] reported a phase III RCT on HIPEC conducted at the National Cancer Center in Korea. In this trial, 184 patients with FIGO stage III-IV who achieved optimal CRS (residual disease $<$1.0 cm) were randomly assigned to either the HIPEC arm or the control arm. Patients in the HIPEC arm received i.p. perfusion with 75 mg/m^2 of cisplatin for 90 min via the closed technique at a temperature of 41.5°C. Both groups were well balanced in terms of stage and NACT use. No differences were observed in the PFS and OS between the two groups regarding survival outcomes.

In 2018, van Driel et al.[6] reported results from a phase III RCT, which investigated the survival benefit from HIPEC in patients with FIGO stage III EOC who received NACT. This trial enrolled 245 patients who showed at least stable disease after three cycles of NACT. They were randomised at the time of surgery in cases in which complete or optimal cytoreduction (residual disease $\leq$1.0 cm) was anticipated. Stratified randomisation was carried out considering previous surgery, institution, and the number of regions involved in the abdominal cavity. Patients in the HIPEC arm received interval CRS and i.p. perfusion with 100 mg/m^2 of cisplatin for 90 min via the open technique at a temperature of 40°C, whereas those in the control arm received interval CRS only. The primary endpoint was the PFS. The HIPEC group showed significantly better PFS (median, 14.2 versus 10.7 months; HR, 0.66; 95% CI, 0.50-0.87; $P = 0.003$) and OS (median, 45.7 versus 33.9 months; HR, 0.67; 95% CI, 0.48-0.94; $P = 0.02$) than the control group. In terms of toxicity, the two groups showed similar proportions of grade 3-4 adverse events (27% versus 25%; $P = 0.76$).[6]

Researchers, however, have raised controversies over van Driel et al.'s[6] RCT.[53-55] Vergote et al. pointed out the following limitations of the study[54]: (i) the sample size was amended during the study from 280 to 240 because of the slow accrual; (ii) the observed PFS of both arms was shorter than that anticipated; (iii) the timing of randomisation might have biased the surgeons carrying out interval CRS in favour of the HIPEC arm; (iv) the final study population was small ($n = 245$); (v) there was an imbalance in histologic types; (vi) the recruitment period was too long (9 years); and (vii) whether the adverse events were reported completely remains controversial.[54] The HIPEC arm clearly showed higher toxicity than the control arm. For example, the rates of any grade infection (18% versus 11%), bowel obstruction (8% versus 3%), thromboembolic events (6% versus 2%), and fever (12% versus 8%) were evidently high.

Moreover, neither *BRCA1/2* mutational status nor maintenance therapy was considered in this study.

In addition, attention must be paid to the role of HIPEC outside of clinical trials. After the publication of van Driel et al.'s[6] phase III RCT, the rate of HIPEC for ovarian cancer increased, although the absolute number of cases remained modest in the USA. Charo et al.[56] reported that 152 ovarian cancer patients underwent HIPEC at 39 hospitals, whereas 20 014 ovarian cancer patients underwent surgery without HIPEC at 256 hospitals in the USA between January 2016 and January 2020. However, HIPEC was associated with increased hospital cost, length of stay, intensive care unit admission, and hospital-acquired complication rates.[56]

The main concerns regarding the use of HIEPC in ovarian cancer are the prolonged operative time, potential toxicity, and postoperative morbidity from HIPEC. However, real-world studies have reported the feasibility and safety of HIPEC after interval CRS. According to an Italian single-centre, prospectively collected cohort study, 34.9% (52/149) of patients with EOC who received interval CRS underwent HIPEC throughout 2019.[57] In this study, HIPEC was administered to not only patients with FIGO stage IIIC disease, but also those with stage IV disease (34.6%), which differed from the study by van Driel et al.[6] All patients in the HIPEC group received i.p. perfusion with 100 mg/m^2 cisplatin via the closed technique at 41°C for 90 min. No differences were observed between the HIPEC and non-HIPEC groups in terms of intraoperative and early postoperative complications. Neither patient recovery nor the time of adjuvant chemotherapy initiation was affected by HIPEC.[57]

According to a Korean single-centre, protocol-based study, 61.5% (40/65) of patients with FIGO stage IIIC-IV EOC underwent paclitaxel and carboplatin combination NACT and interval CRS.[58] After the interval CRS, HIPEC was administered to patients who achieved optimal cytoreduction (residual disease $\leq$1.0 cm) unless (i) complete remission was achieved after NACT, (ii) excessive bleeding occurred during surgery, or (iii) patient refused to undergo the procedure. In this way, 67.5% (27/40) of the patients who underwent NACT and interval CRS received HIPEC, consisting of i.p. perfusion of paclitaxel 175 mg/m^2 at an inflow temperature of 42°C for 90 min. In terms of perioperative complications, 18.5% of the patients who received interval CRS plus HIPEC experienced major complications, defined as MSKCC grade $\geq$III. Two patients required secondary surgical revision, and none of the patients died within 30 days postoperatively.[58] Both Italian and Korean real-world studies have shown that HIPEC at the time of interval CRS is feasible, without an increase in the rate of complications or deterioration in the patient's condition after surgery.

To the best of our knowledge, the effect of HIPEC on survival outcomes remains undetermined in patients with advanced EOC who are candidates for primary CRS. An ongoing phase III RCT, OVHIPEC-2, will address this question.[59] This trial investigates whether the addition of HIPEC to primary CRS would improve the survival outcomes of patients with FIGO stage III EOC. The primary endpoint is the OS. After complete or near-complete (residual disease $\leq$2.5 mm) cytoreduction, randomisation is conducted in the operating room. Patients are randomly assigned to either the HIPEC arm, treated with cisplatin 100 mg/m^2 perfusion at 40-41°C for 90 min, or the no HIPEC arm. All patients receive six cycles of carboplatin-paclitaxel chemotherapy every 3 weeks and, if indicated, maintenance therapy with bevacizumab or PARP inhibitor according to the current guidelines. A total of 538 patients will be enrolled, and primary analyses are anticipated in 2026. Subgroup analyses will include institute, initial peritoneal cancer index, completeness of surgery, histological subtype, and germline and somatic *BRCA1/2* mutations.

With regard to the role of HIPEC in the management of ovarian cancer, some physicians argue that evidence of HIPEC as upfront treatment is still insufficient; improvement in survival has been prospectively demonstrated only at interval CRS by a single RCT and needs to be confirmed.[60,61] Consistently, the Consensus Conference of the European Society for Medical Oncology and ESGO held in 2018 also concluded that HIPEC is not a standard first-line treatment (level of evidence: II, strength of recommendation: A).[23] Nevertheless, according to the National Comprehensive Cancer Network guidelines, HIPEC with 100 mg/m^2 of cisplatin can be considered during interval CRS for FIGO stage III disease.[62] HIPEC is also included in the Netherlands' national guidelines; HIPEC with 100 mg/m^2 cisplatin can be considered after complete or optimal interval CRS as treatment of FIGO stage III disease. However, no adequate RCTs have established HIPEC as the standard care for recurrent disease.[63] Moreover, the effect of HIPEC when combined with bevacizumab or PARP inhibitor maintenance and other novel therapeutic agents remains uncertain. Thus, further studies are needed to explore ways to maximise the therapeutic effect of HIPEC in each disease setting.

CONCLUSIONS

In this article, we reviewed the current role of surgery and HIPEC in the management of EOC. The standard surgical treatment of advanced EOC is upfront CRS, which aims to complete resection of all macroscopic diseases. For selected patients, NACT followed by interval CRS may be considered an alternative treatment strategy. Secondary CRS may have a survival benefit in patients with recurrent, platinum-sensitive ovarian cancer when complete resection is achieved. A multi-dimensional evaluation of an individual's status, extent of disease, and resectability is necessary. The surgical capacity of gynaecologic oncologists and surgeons at the right centre is also critical, as they directly influence the complete cytoreduction rate of patients. HIPEC can be considered after optimal interval CRS as treatment of FIGO stage III disease, but further studies are warranted. The efficacy of HIPEC should be evaluated in various disease settings.

Both surgery and HIPEC have evolved over time. Results from landmark studies on these issues have been and are

continuously being published, and we look forward to the results of ongoing clinical trials. We do not presume that the role of surgery and HIPEC in ovarian cancer will decrease owing to the advent of PARP inhibitors, immune checkpoint inhibitors, and new targeted agents. Instead, more individualised management will be feasible by selecting surgical candidates delicately and combining surgery and HIPEC with new drugs and maintenance therapy. Thus, improvement in survival outcomes is expected in patients with ovarian cancer.

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DISCLOSURE

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