Treatment of Primary Epithelial Ovarian Cancer

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Maximal cytoreduction and platinum-based chemotherapy remain the mainstay treatments for epithelial ovarian cancer. New modalities include targeted therapy, intraperitoneal chemotherapy, and hyperthermic intraperitoneal chemotherapy. With different characteristics in different patients and the complexity of diseases, treatment should be individualised and reviewed by a multidisciplinary team.

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Introduction

Ovarian cancer is the seventh most common cancer among women globally[1]. In 2015 in Hong Kong, ovarian cancer was the sixth most common cancer among women and the seventh most common cause of cancer death among women[2]. There were 578 new cases of ovarian cancer (median patient age, 52 years), accounting for 3.9% of all cancer cases. The lifetime risk before age 75 years was 1 in 107.

Most epithelial ovarian cancers are diagnosed at a late stage[3]. Despite cytoreductive surgery and platinum-based chemotherapy, more than half of patients with advanced disease have recurrence and a poor prognosis[4,5]. We review the management of primary epithelial ovarian cancers.

Early-stage Epithelial Ovarian Cancers

Ovarian cancer is staged according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system. Pre-operative imaging such as chest radiography, computed tomographic and magnetic resonance imaging of the abdomen and pelvis, and positron emission tomography computed tomography are commonly used to assess the extent of disease and the feasibility of complete debulking of the tumour.

In apparently early-stage disease, the standard treatment is staging laparotomy, which can serve diagnostic and treatment purposes. After a midline skin incision, the procedure comprises peritoneal washing for cytology, exploration of the whole abdomen and pelvis, total abdominal hysterectomy and bilateral salpingo-oophorectomy, pelvic and para-aortic lymphadenectomy, omentectomy, peritoneal biopsies, and biopsy of any suspicious lesions. Fertility-sparing surgery (unilateral salpingo-oophorectomy, full staging, and endometrial sampling) can only be considered if the disease is at clinical stage 1 and the histology is relatively indolent such as low-grade serous carcinoma, low-grade endometrioid carcinoma, or mucinous carcinoma.

Minimally invasive surgery may be considered in selected patients[6]. In a meta-analysis of five comparative studies[7], compared with laparotomy, laparoscopy resulted in less blood loss (mean difference [MD], -175.7 ml; 95% confidence interval [CI], -219 to -132.3 ml), longer operative time (MD, 16.8 min; 95% CI, 8.8-24.8 min), shorter length of hospitalisation (MD, -3.3 days; 95% CI, -3.9 to -2.7 days), and earlier commencement of adjuvant chemotherapy (MD, -4.9 days; 95% CI, -6.7 to -3.2 days). Laparotomy and laparoscopy were comparable in terms of the rates of spillage (7.2% vs. 9.5%; 95% CI, 0.35-1.73), upstaging (17.1% vs. 16.6%; 95% CI, 0.38-1.27), and recurrence (5.3% vs. 8.3%; 95% CI, 0.21-1.21). The incidence of port-site metastasis ranges from 0.89% to 17%[8,9]. Independent risk factors for abdominal wall metastasis are FIGO stage 4 (compared with stage 3) and the presence of ascites of >500 ml. Minimally invasive surgery is an acceptable option for small-volume disease.

After surgery, platinum-based chemotherapy is given to high-risk patients, including those with stage 1C disease or beyond and those with more aggressive tumours such as high-grade endometrioid carcinoma, high-grade serous carcinoma, small cell carcinoma, and carcinosarcoma.

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Late-stage Epithelial Ovarian Cancers

The treatment options depend on the chance of optimal or complete debulking, patient fitness, and surgical morbidity[10]. There are two main options: (1) primary debulking surgery (PDS) followed by adjuvant chemotherapy, and (2) neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) with or without further adjuvant chemotherapy.

The definition of optimal cytoreduction has changed from ≤2 cm to ≤1 cm (R1); complete debulking refers to no gross macroscopic disease (R0)[10]. Different models have been proposed to predict the possibility of achieving optimal cytoreduction and to identify patients whose disease is unlikely to be optimally debulked. Computed tomography has been used to predict the presence of residual disease[11-13]. Nonetheless, most models have not been systematically validated and the accuracy is around 34% to 77%. The Fagotti model of laparoscopic assessment has been validated and is most commonly used; it comprises seven parameters: the presence of omental cake, peritoneal, and diaphragmatic carcinomatosis, mesenteral retraction, bowel and stomach infiltration, and liver metastasis (Table 1)[14]. The presence of each parameter is allocated two points. A total score of ≥8 indicates zero probability of optimal debulking at laparotomy, with an overall accuracy rate of 77.3% to 100%[15].

Primary debulking surgery

For patients with advanced disease, the aim of upfront surgery is to achieve maximal cytoreduction. There is robust evidence on the survival benefit after complete or optimal debulking. In patients with stage 3 to 4 ovarian cancer who underwent PDS and subsequent platinum-based chemotherapy, each 10% increase in the maximal cytoreduction led to a 5.5% increase in median survival time[16]. For each 10% increase in the proportion of patients who achieved R0 or R1, the median survival time increased 2.3 and 1.8 months, respectively[17]. In a Cochrane review of the effectiveness and safety of optimal PDS for advanced ovarian cancer[18], complete cytoreduction was associated with prolonged overall survival and progression-free survival; such survival benefit was observed in patients with optimal cytoreduction with residual disease of <1 cm, compared with those with suboptimal (>1 cm) debulking.

To achieve R0, extensive pelvic and upper abdominal procedures (diaphragmatic surgery, liver resection, splenectomy, pancreatomy, porta hepatis dissection, and bowel resection) may be necessary. The rate of these procedures has increased in the United States[19], as has the optimal debulking rate[20]. The rates of complications (haemorrhage, vascular injury, nerve injury, and prolonged hospitalisation) are lower in high-volume hospitals than in low- and medium-volume hospitals (10.2% vs. 21.2% vs. 21.7%, p=0.01)[19]. In a retrospective review of 620 patients, 138 (22.3%) developed grade ≥3 complications and 55 (8.9%) died within 90 days of surgery[21].

Systematic Lymph Node Dissection

In a randomised trial that compared the survival outcomes of 427 patients with stage 3B to 4 disease[22], compared with debulking of enlarged lymph nodes only, systematic lymph node dissection improved the 5-year progression-free survival (31.2% vs. 21.6%; 95% CI, 1.5%-21.6%) but not the 5-year overall survival (48.5% vs. 47%; 95% CI, -8.4% to 10.6%) in patients with optimally debulked ovarian cancer. The intra-operative complication rates were similar in both arms, but the rates of post-operative lymphocysts and lymphoedema were higher in those with systematic lymph node dissection.

In the Lymphadenectomy In Ovarian Neoplasm study that randomised 647 patients with stage 2B to IV disease (who had no clinical lymph node involvement with apparently R0 at PDS) to undergo systematic lymph node dissection or not, the preliminary results presented at the American Society of Clinical Oncology meeting in 2017

Table 1. Fagotti laparoscopic scoring system[14]

Parameter	Score	Remark
Peritoneal carcinomatosis (massive unresectable/ military pattern)	2	Score 0 if carcinomatosis involving limited area that are surgically removable by peritonectomy
Diaphragmatic disease	2	-
Mesenteric disease	2	Score 0 if small nodules that are potentially treated by argon beam coagulator
Omental disease	2	Score 0 if isolated localisation
Bowel infiltration	2	-
Stomach infiltration	2	-
Liver metastasis	2	Any surface lesion

revealed that the two groups were comparable in terms of median overall survival and progression-free survival. It appears legitimate to omit systemic lymph node dissection and debulk only enlarged lymph nodes to achieve R0.

Adjuvant chemotherapy

Platinum-based chemotherapy is the standard adjuvant treatment for advanced epithelial ovarian cancers. The most commonly used regimen is 3-weekly carboplatin and paclitaxel. The role of dose-dense chemotherapy has been evaluated.

In the Japanese Gynecologic Oncology Group (GOG) 3016 study[23], in patients with stage 2 to 4 epithelial ovarian cancers, compared with the conventional 3-weekly regimen, the use of dose-dense paclitaxel (80 mg/m^2) once a week (on day 1, 8, and 15) combined with carboplatin (area under curve, 6) on day 1 of a 21-day cycle improved the progression-free survival (28.2 vs. 17.5 months, p=0.0037) and overall survival (100.5 vs. 62.2 months, p=0.039), although the rate of anaemia was higher in the dose-dense group (69% vs. 44%, p<0.0001).

However, such survival benefit could not be demonstrated by the Multicentre Italian Trials in Ovarian cancer (MITO) 7 study[24], which used a lower dosage in the dose-dense regimen and included stage 1C patients. The MITO-7 study showed a lower incidence of grade 3-4 neutropenia, neutropenic fever, grade 3-4 thrombocytopenia, and grade ≥2 neuropathy in the dose-dense arm than the conventional arm.

The GOG-262 trial compared progression-free survival of patients who received either dose-dense or conventional carboplatin and paclitaxel with or without bevacizumab[25]. For those who did not receive bevacizumab, progression-free survival was longer in the dose-dense arm than the conventional arm (14.2 vs. 10.3 months, p=0.03). For those received bevacizumab, no difference in progression-free survival was seen.

In the International Collaborative Ovarian Neoplasm (ICON) 8 study that randomised patients with stage 1C to 4 epithelial ovarian / peritoneal / fallopian tube carcinoma in a 1:1:1 ratio into 3-weekly carboplatin and paclitaxel, 3-weekly carboplatin and weekly paclitaxel, or weekly carboplatin and paclitaxel, the preliminary results reported in the European Society for Medical Oncology 2017 Congress showed that there was no difference in progression-free survival[26]. The ICON 8b study included only stage 3 to 4 patients and they were randomised to a conventional regimen with bevacizumab, dose-dense regimen, or dose-dense with bevacizumab.

Targeted Therapy

Bevacizumab is an intravenously administered target therapy; it is a recombinant humanised monoclonal IgG1 antibody that neutralises vascular endothelial growth factor A. It acts via two mechanisms. First, it inhibits neovascularisation and regresses existing microvessels and hence suppresses tumour growth. Second, it improves the structure and function of the tumour vessels that in turn improves the delivery of chemotherapeutic agents to the tumour.

In the GOG 218 trial that randomised patients with suboptimally debulked stage 3 or 4 ovarian cancer to receive standard adjuvant intravenous paclitaxel / carboplatin, chemotherapy with five cycles of concurrent bevacizumab (15 mg/kg), or chemotherapy with concurrent bevacizumab and subsequent bevacizumab maintenance for 16 more cycles[27], the median progression-free survival was 10.3, 11.2, and 14.1 months, respectively, and the overall survival of the three groups was similar.

The ICON 7 study randomised patients with high-risk early-stage disease or FIGO stage 2B to 4 disease that was optimally or suboptimally debulked to either standard adjuvant paclitaxel / carboplatin, or concurrent bevacizumab (7.5 mg/kg) with chemotherapy with maintenance bevacizumab up to 12 more cycles or until disease progression[28,29]. Progression-free survival at 42 months for suboptimally debulked stage 3 or 4 patients was 14.5 and 18.1 months, respectively (p=0.04), and the median overall survival was 28.8 and 36.6 months, respectively (p=0.002). Bevacizumab was well tolerated with adverse effects of hypertension, proteinuria, delayed wound healing, fistula and bowel perforation, and a small risk of thromboembolic events.

Other than bevacizumab, olaparib, a poly (ADP-ribose) polymerase inhibitor, has also been investigated in the SOLO-1 study[30]. Patients with stage 3 (with one attempt at optimal debulking) or stage 4 (either following PDS or IDS) disease who had a *BRCA* mutation and responded to first-line platinum-based chemotherapy were randomised to receive olaparib tablet maintenance or placebo. Preliminary results showed that olaparib improved progression-free survival. The GINECO/ENGOTov25 PAOLA-1 Trial evaluates a combination of olaparib and bevacizumab as maintenance therapy in women with newly diagnosed advanced ovarian cancer irrespective of their *BRCA* status[30]. Results are expected to be published in 2019.

Intraperitoneal chemotherapy

The peritoneal cavity is a common site of metastasis in epithelial ovarian cancers. Intraperitoneal (IP) chemotherapy exerts its cytotoxic effect both locally and systemically. Locally, the drug can directly penetrate the tumour mass on the peritoneal surface by free-surface diffusion[31], but the depth of penetration is a few millimetres only[32]. Systemically, the drug enters the circulation through uptake by the peritoneum and passage through the portal circulation, and reaches the tumour through capillary flow[31]. This enables delivery of a higher dose of the chemotherapeutic agent to the tumour while minimising systemic toxicity[33-39]. Because of the limited depth of direct penetration of chemotherapeutic agents, IP chemotherapy is more likely to benefit those with microscopic disease or low-volume residual disease of <0.5-1 cm[32].

Compared with IV chemotherapy alone, IP chemotherapy (with cisplatin) increased overall survival by 10 to 16 months in patients with advanced ovarian cancer (Table 2)[40-42]. The National Cancer Institute states that women with stage 3 ovarian cancer who have undergone optimal cytoreduction should be considered for IP chemotherapy. Carboplatin is less toxic than cisplatin and is the standard drug for IV chemotherapy for ovarian cancer. IP chemotherapy with carboplatin combined with a dose-dense IV paclitaxel regimen has been investigated in the Japanese iPOCC study, with results expected to be available in 2019[43].

Despite the promising results of IP chemotherapy, it is not widely adopted, mainly because of its high toxicity. Patients who received IP chemotherapy experienced greater haematological, gastrointestinal, and metabolic toxicities than those who received IV chemotherapy (Table 2)[41,42]. In the GOG 172 study, only 42% of patients in the IP arm could complete six cycles of IP chemotherapy, with catheter-related complications being the primary reason for discontinuation[42]. A Cochrane review also demonstrated that compared with IV chemotherapy, IP chemotherapy was associated with more severe adverse events such as gastrointestinal toxicities (e.g. bowel obstruction), pain, fever, and infection[44]. Another barrier to IP chemotherapy is the increased costs related to more complicated logistics[45].

Neoadjuvant Chemotherapy

For patients with a poor condition or whose disease is so extensive that optimal debulking is not feasible, NACT may be an alternative. A biopsy or at least a cytological sample with adequate cell numbers for immunostaining is mandatory before NACT. After 3 to 4 cycles, IDS is performed if there is a good response and further chemotherapy may be required.

The European Organisation for Research and Treatment of Cancer 55971 trial compared the outcomes of platinum-based NACT followed by IDS and additional chemotherapy with conventional treatment of PDS followed by platinum-based chemotherapy in 632 patients

Table 2. Intraperitoneal (IP) versus intravenous (IV) chemotherapy in overall survival and progression-free survival

Study	Eligible patients	Interventions	IP vs. IV chemotherapy		Toxicity
			Overall survival, m	Progression-free survival, m	
GOG 104[40]	Stage 3; residual ≤2 cm; n=546	Control arm: IV cisplatin (100 mg/m^2) + IV cyclophosphamide (600 mg/m^2); experiment arm: IP cisplatin (100 mg/m^2) + IV cyclophosphamide (600 mg/m^2)	49 vs. 41, p=0.02	-	Toxicity more frequent in IV group (moderate to severe tinnitus, clinical hearing loss, neuromuscular toxic effects)
GOG 114[41]	Stage 3; residual ≤1 cm; n=462	Control arm: IV paclitaxel (135 mg/m^2, 24 h) + IV cisplatin (75 mg/m^2); experiment arm: IV carboplatin (area under curve, 6) every 28 days for 2 courses), then IV paclitaxel (135 mg/m^2, 24 h) + IP cisplatin (100 mg/m^2)	63 vs. 52, p=0.05	28 vs. 22, p=0.01	Neutropenia, thrombocytopenia, and gastrointestinal and metabolic toxicities were greater in the IP arm
GOG 172[42]	Stage 3; residual ≤1 cm; n=415	Control arm: IV paclitaxel (135 mg/m^2, 24 h) + IV cisplatin (75 mg/m^2); experiment arm: IV paclitaxel (135 mg/m^2, 24 h) + IP cisplatin (100 mg/m^2) + IP paclitaxel (60 mg/m^2) on day 8	65.6 vs. 49.7, p=0.03	23.8 vs. 18.3, p=0.05	Grade 3 or 4 pain, fatigue, hematologic, gastrointestinal, metabolic and neurologic toxic effects were more common in IP group

with stage 3C or 4 ovarian cancer[46]. Patients in the NACT arm had similar survival rates but a lower incidence of surgical morbidity (severe haemorrhage, infection, and venous thromboembolism) than patients in the PDS arm. The CHORUS trial also demonstrated a non-inferiority of NACT and IDS in comparison to PDS and adjuvant chemotherapy in terms of median overall survival (22.6 vs. 24.1 months, p>0.05)[47]. The NACT groups had fewer major postoperative adverse events (14% vs. 24%, p=0.0007) and deaths (<1% vs. 6%, p=0.001). Similarly, the SCORPION trial showed that NACT was associated with less perioperative major morbidity (52.7% vs. 5.7%, p=0.0001) and better quality of life, compared with conventional treatment[48].

Nevertheless, results should be interpreted with caution. Patient characteristics were heterogeneous between different study groups, as were the skill and experience of the surgeons. The optimal treatment option for advanced epithelial ovarian cancer remains controversial[49]. PDS can reduce the tumour load in a short time before chemotherapy and may reduce the risk of developing chemo-resistance, whereas NACT may shrink the tumour and reduce peri-operative morbidity and help evaluate the response to the chemotherapy and identify any non-responders early so as to modify the drug regimen.

The ANTHALYA trial showed that bevacizumab, together with carboplatin and paclitaxel, could achieve a 58.6% complete resection rate at IDS, compared with the pre-defined complete resection rate of 45% and the complete resection rate of 51.4% in the chemotherapy alone arm[50]. Bevacizumab resulted in more grade ≥3 toxicities but the pre-specified safety threshold was not reached. Preliminary results showed that the response rate and progression-free survival could be improved for those with stage 3C or 4 ovarian, tubal, or peritoneal carcinoma not eligible for PDS[51]. Further investigation is required to establish safety and efficacy of bevacizumab in neoadjuvant chemotherapy.

Interval debulking surgery

The aim of IDS is to debulk all tumours to R0 as in PDS. The optimal timing of IDS should be based on the health of the patient, recovery from any chemotherapy-related toxicity, especially myelosuppression, and the likelihood of achieving optimal debulking. A decrease in cancer antigen 125 level and the disappearance of clinical ascites were predictors of complete cytoreduction[52-54]. Nonetheless, no prospective trials have examined the role of systematic lymph node dissection in IDS. A case-control study showed that there was no difference in 2-year survival (69% vs. 88%, p=0.0777), recurrence (70.0% vs. 62.4%, p>0.05), or death (30% vs. 23.7%, p>0.05) between systematic lymph node dissection and debulking of enlarged nodes only at the time of IDS with R1 residual disease[55].

Hyperthermic intraperitoneal chemotherapy

Distinctly different to postoperative IP chemotherapy, hyperthermic intraperitoneal chemotherapy (HIPEC) involves a single administration of heated chemotherapeutic agents into the peritoneal cavity at the time of cytoreductive surgery, followed by conventional IV chemotherapy. Compared with normothermic IP chemotherapy, HIPEC has following advantages. First, the use of heat can increase the cytotoxic effects of chemotherapeutic drugs by directly inducing thermal cellular damage, increasing DNA-crosslinking and increasing drug penetration into tumour cells[56-58]. Second, hyperthermia has been shown to increase the sensitivity of tumour cells to cisplatin in both platinum-sensitive and resistant cell lines[59]. Third, by giving chemotherapy intra-operatively, drugs can disperse to all areas of the peritoneal cavity without being hindered by adhesions. Surgeons can also control the dwell time and optimise the drug exposure in the peritoneal cavity. Cytoreductive surgery and HIPEC have been well-established for the treatment of peritoneal carcinomatosis in gastrointestinal malignancies, peritoneal mesothelioma, and pseudomyxoma peritonei. Nonetheless, its role in ovarian cancer has only recently been examined.

In a meta-analysis that included nine comparative studies and 28 cohort studies, cytoreduction and HIPEC followed by chemotherapy achieved a significantly better overall survival than cytoreduction and chemotherapy alone, and the benefit continued for up to 8 years in primary disease, and up to 3 years in recurrence disease[60]. The mortality and morbidity rates were similar in both groups. A multicentre phase III trial showed that the addition of HIPEC with cisplatin to IDS resulted in longer recurrence-free survival (10.7 vs 14.2 months) and overall survival (33.9 vs 45.7 months) than surgery alone, and the addition of HIPEC did not result in higher rates of adverse events[61]. Many centres in the world increasingly adopt HIPEC following NACT.

Conclusion

Maximal cytoreduction and platinum-based chemotherapy remain the mainstay treatments for epithelial ovarian cancer. New modalities include targeted therapy, IP chemotherapy, and HIPEC. With different characteristics in different patients and the complexity of diseases, treatment should be individualised and reviewed by a multidisciplinary team.

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