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REVIEW ARTICLE

Is peritonectomy and hyperthermic intraperitoneal chemotherapy a new standard of treatment for advanced epithelial ovarian cancer?

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Ovarian cancer is the leading cause of death due to gynaecological malignancy with a five-year relative survival of only 20–30% for Australian women with stage 3 and 4 disease. Most cases present with spread of cancer cells outside the pelvis to the peritoneal surfaces of the abdomen and associated viscera. Efforts to improve survival from advanced disease have therefore led to more extensive cytoreductive surgery, including the use of peritonectomy surgery, which is usually combined with hyperthermic intraperitoneal chemotherapy (HIPEC). There is an increased interest in this treatment approach by gynaecological oncologists, particularly after the results of a recent randomised controlled trial (RCT) from the Netherlands showed improved survival in women who were given HIPEC at the time of cytoreductive surgery for primary disease. This article discusses the technique of peritonectomy and HIPEC, the evidence for its use, and the potential role of this treatment approach for advanced epithelial ovarian cancer in Australian centres.

KEYWORDS

chemotherapy, cytoreductive surgical procedures, hyperthermia, ovarian neoplasms, peritoneal neoplasms

INTRODUCTION

Ovarian cancer is the leading cause of death due to gynaecological cancer in Australia with an estimated 1580 women diagnosed and 1047 women dying from this disease in 2017.[1] Most patients (70%) present with advanced carcinomatosis, with the primary tumour originating from the epithelium of the ovary, fallopian tube or peritoneum and then spreading (with the patient experiencing few initial symptoms) to the peritoneal surfaces and viscera of the pelvis and abdomen. The five-year relative survival for women diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage 3 and 4 epithelial ovarian cancer (EOC) has changed little and remains around 20–30%.[2] An effort to improve survival for women with EOC around the world has led to new therapeutic approaches and the relentless search for molecular targeted treatments. Peritonectomy followed by hyperthermic intraperitoneal chemotherapy (HIPEC) is a combined treatment approach for peritoneal carcinomatosis that, up until 2017, was not commonly used for ovarian cancer in Australia. Recently there has been greater interest in this treatment by gynaecological oncologists since the first randomised controlled trial (RCT) of HIPEC for primary ovarian cancer was published in January 2018,[3] with results showing improved survival for women receiving neoadjuvant chemotherapy (NAC) followed by cytoreductive surgery with HIPEC compared to cytoreductive surgery without HIPEC, followed by intravenous (IV) chemotherapy in both arms. It is likely that this treatment will become more widely used but the role of peritonectomy and HIPEC for ovarian cancer will only be determined after ongoing high-quality clinical trials have been completed.

A MOVE TOWARD MORE EXTENSIVE CYTOREDUCTIVE SURGERY FOR OVARIAN CANCER

The current standard of treatment for most women with a primary diagnosis of advanced EOC treated in Australia is 'optimal' surgical cytoreduction by a certified gynaecological oncologist (CGO), followed by adjuvant combined platinum-paclitaxel chemotherapy. Although the definition of 'optimal' cytoreduction has been historically defined by the Gynecologic Oncology Group as <1 cm residual disease following surgery,[4] accumulating evidence supports complete cytoreduction to zero residual as the goal of surgery for primary disease[5,6] and carefully selected cases of recurrence.[7,8] Around the world, centres that have incorporated more extensive resection of tumours from the upper abdominal peritoneum, diaphragm and viscera have been able to show significant improvements in rates of complete cytoreduction, coinciding with improved rates of survival and acceptable rates of morbidity.[9,10] Similarly in Australia, there has been a shift by gynaecological oncologists toward more extensive surgery for advanced ovarian cancer over the past decade.[11]

WHAT IS A PERITONECTOMY AND HOW IS IT DIFFERENT FROM CURRENT OVARIAN CANCER SURGERY?

Aggressive surgical management of patients with peritoneal malignancy was pioneered by Sugarbaker in the 1980–90s.[12] The procedure was initially developed for the treatment of disseminated peritoneal malignancy due to appendiceal cancer. Since that time, peritonectomy has been used for the management of other disseminated peritoneal malignancies including colorectal cancer,[13,14] appendiceal pseudomyxoma peritonei (PMP),[15] and peritoneal mesothelioma.[16] The peritonectomy technique has been standardised and described in detail by Sugarbaker[17] with modifications by other peritonectomy groups.[18] The peritonectomy procedure for ovarian cancer has been developed similarly, with the aim of achieving complete cytoreduction (CC0) using peritoneal and visceral resections where required. The surgical procedure varies from the traditional 'debulking' approach used by gynaecological oncologists in that it is based on a systematic approach to record the volume of tumour using the peritoneal cancer index (PCI) and then remove all macroscopic disease in well-defined abdominal and pelvic regions, as shown in Table 1.

The disease extent and distribution are first assessed and recorded using the Peritoneal Cancer Index (PCI), as developed by Sugarbaker[12] and shown in Figure 1. A score for the amount of disease (0–3) is recorded from 13 different regions of the abdominal and pelvic cavity, with a highest possible score of 39. Depending on the peritoneal involvement, up to six peritonectomy procedures, with associated possible visceral resections (shown in Table 1), may be performed to remove the disease. The extent of resection is determined by the 'biological aggressiveness' of the disease, which in turn reflects the histologic subtype.[18] For example, high-grade serous cancers of the ovary (which account for around 70% of EOC[19]) spread in a 'random proximal distribution', usually requiring multiple partial peritonectomy procedures, whereas mucinous cancers of the ovary spread in a 'widespread cancer distribution', requiring a more aggressive and complete peritonectomy.[20]

SHOULD ALL CASES OF ADVANCED OVARIAN CANCER HAVE A PERITONECTOMY?

Despite the world-wide trend to perform more aggressive cytoreductive surgery for ovarian cancer, there is a lack of high-level evidence for this approach.[21] There are currently no published randomised trials directly comparing 'radical' and standard surgery, and most studies are retrospective analyses of patient cohorts from single institutions.[22,23] An important factor to consider is the potential for increased rates of post-operative morbidity, which can delay adjuvant chemotherapy for what is, in most cases, a chemotherapy-sensitive disease. The rate of complications following peritonectomy surgery can be considerable, particularly when multiple visceral resections are required.[24] Rates

TABLE 1 Abdominal regions, peritonectomies, and visceral resections which may be required during peritonectomy surgery for peritoneal carcinomatosis (from Deraco M *et al.* 2009,[18] with permission)

Abdominal region	Peritonectomies	Visceral resections
Right upper	Right sub-phrenic peritonectomy Glisson's capsule dissection	
Left upper	Left sub-phrenic peritonectomy	Gastrectomy
Antero-lateral	Stripping of para-colic gutters Greater omentectomy	Splenectomy, distal pancreatectomy Appendectomy, right colectomy
Sub-hepatic	Lesser omentectomy Stripping of the omental bursa	Gastric antrectomy Cholecystectomy
Pelvis	Pelvis peritonectomy	Sigmoidectomy Hysterectomy, bilateral adnexectomy

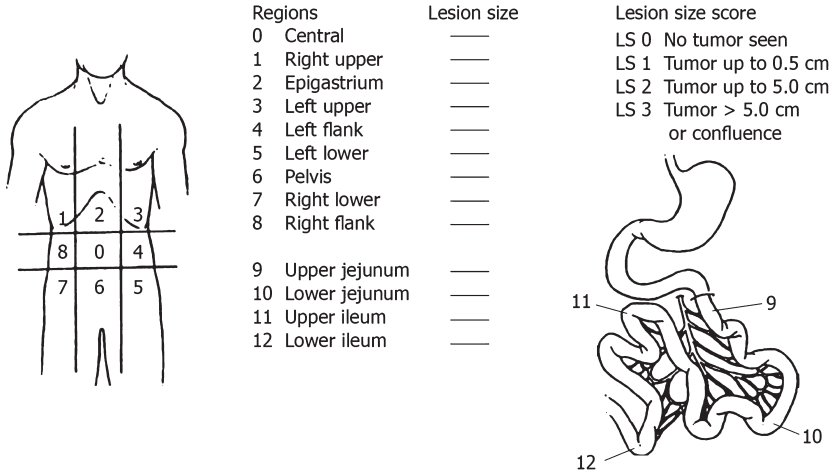

FIGURE 1 Peritoneal Cancer Index (as devised by Sugarbaker[12] and published by Gilly,[46] with permission).

of morbidity and mortality will be highly dependent on the skill of the surgical team and the standard of peri-operative care.

Outcomes are best when this surgery is performed in high-volume centres by experts working within a multidisciplinary surgical and critical care team, supporting the argument for centralisation of care. With an increased need for intensive care unit stay post-operatively and an overall median hospital stay of 18 days (8–24 days) following peritonectomy and HIPEC,[25] sufficient resource allocation is vital.

Most published studies of peritonectomy for ovarian cancer have highlighted the importance of pre-operative tumour load (measured by the peritoneal cancer index or PCI) as being predictive of survival outcomes. In colorectal cancer, a cut-off for PCI between 10 and 20 has been used to determine whether peritonectomy surgery is worthwhile.[26,27] For pseudomyxoma peritonei from low-grade appendiceal tumours, there is no such PCI cut-off as this tumour has a less aggressive biological behaviour.[28] Although there is no defined cut-off for ovarian cancer, findings such as extensive small bowel involvement which would result in short bowel syndrome if resected, or the predicted inability to achieve a CC0-CC1 resection (<2.5 mm in largest diameter disease), are considered to be contra-indications to peritonectomy surgery.

Two randomised studies currently underway which may help to answer the question of when aggressive cytoreductive surgery should be used for ovarian cancer are the Scorpion trial[29] and the TRUST study.[30] Both studies compare primary surgery (PS) to neoadjuvant chemotherapy and interval debulking surgery (NAC-IDS) using aggressive surgical procedures in women with advanced disease. The authors of the Scorpion trial,[29] a single-centre Italian study, have published the final analysis of peri-operative outcome in terms of early (≤30 days) and late (between one and six months) major post-operative complications. Radical surgical procedures such as diaphragmatic stripping/resection, splenectomy, distal pancreatectomy and gastrectomy, and rectosigmoid resection were required in 100% of PS cases compared to 48.1% of NAC-IDS cases. Rates of moderate and severe post-surgical morbidity were significantly higher in the PS arm compared to the NAC-IDS arm at 30 days (52.7% vs 5.8%, $P = 0.0001$) and between one and six months (15.1% vs 0%, $P = 0.004$), respectively. The rate of death was also higher in the PS arm than the NAC-IDS arm at 30 days (3.6% vs 0%) and between one and six months (1.8% vs 0%). Quality of life scores were lower in women who had PS in a number of domains, including emotional and cognitive functioning, and physical functioning in the areas of nausea/vomiting, dyspnoea and insomnia.

The survival outcomes for the Scorpion trial are not yet mature, but the results will need to show a significant survival benefit in the PS (more radical surgery) arm to support its use over NAC-IDS. The results of the TRUST study,[30] a similar but much larger multi-centred international trial, will be available in 2023. The results from these trials will improve our understanding of the role of aggressive cytoreductive surgery for advanced ovarian cancer.

WHAT IS HIPEC?

HIPEC is usually given immediately following the peritonectomy procedure with the aim of directly delivering a heated cytotoxic drug to the peritoneal surface of the abdomen and pelvis. While cytoreductive surgery removes macroscopic disease, the purpose of HIPEC is to eradicate microscopic disease from the peritoneal cavity. Studies have shown that hyperthermia enhances penetration of the chemotherapy agent and induces tumour cell death by multiple mechanisms, including impairing DNA repair, inhibiting angiogenesis, and inducing apoptosis.[31,32] Delivering chemotherapy directly to the peritoneal surfaces allows for a much higher concentration of the drug into the tumour cells by direct diffusion compared to systemic delivery by the intravenous route, thereby improving cytotoxicity while limiting systemic adverse effects.[33] The treatment rationale is that HIPEC can penetrate and eradicate tumours up to 2.5 mm in greatest diameter, so that residual disease should be, where possible, less than 2.5 mm for HIPEC to be most effective.

The technique of giving HIPEC has evolved since the development of the first thermal transfusion infiltration system (TIFS) for delivery of heated chemotherapy into the peritoneal cavity of a human by Spratt in the 1970s.[34] The current method involves heating chemotherapy to a temperature of approximately 42 (41–43)°C (using an external heat pump), with instillation of the chemotherapy into the peritoneal cavity using either an open (colosseum), closed, or semi-open technique. Infusion catheters are usually removed immediately following the procedure. The HIPEC procedure therefore has the advantage of avoiding the complications associated with long-term catheter placement that have hampered the uptake of adjuvant post-operative IP chemotherapy in many centres, including those in Australia.[35]

WHAT IS THE EVIDENCE FOR HIPEC FOR ADVANCED OVARIAN CANCER?

Until recently, most of the evidence for HIPEC in the treatment of advanced ovarian cancer was based on large retrospective series,[36–38] a few small non-randomised prospective studies,[39,40] and a small randomised trial of low quality in regard to study design.[41] The outcomes were difficult to measure as the study groups were heterogenous due to the combined inclusion of both primary and recurrent disease, different extent of peritonectomy surgeries performed, and various FIGO stages and types of histology included. Huo *et al*.[25] performed a systematic review and meta-analysis of published trials in 2015 and identified nine comparative studies, reporting an improvement in survival following CRS and HIPEC (±IV chemotherapy) compared to CRS alone (±IV chemotherapy). Morbidity following CRS and HIPEC was reported to be between 12% and 33%.[25,42] The majority of complications are likely to be due to the aggressive CRS rather than HIPEC, particularly in respect to bowel complications (anastomotic leak, bowel fistula, sepsis and wound breakdown/dehiscence), while the addition of HIPEC is associated with haematological toxicity due to transient bone marrow suppression, and renal impairment.

The results from the first RCT of HIPEC for primary ovarian cancer were published in January 2018 in *The New England Journal of Medicine*.[3] The research team included peritonectomy surgeons and gynaecological oncologists working at eight specialised centres within the Netherlands, all centres having previous experience in, giving HIPEC for other carcinomatoses. The study was a multicentre randomised open-label phase III trial, designed to assess the efficacy and safety of CRS and HIPEC compared to CRS alone, followed by IV chemotherapy, in patients with a first diagnosis of stage III epithelial ovarian/tubal/peritoneal cancer that was deemed too extensive for up-front surgery or who had received incomplete primary surgery. All 245 participants received neoadjuvant chemotherapy and had at least stable disease after three cycles of carboplatin and paclitaxel before undergoing CRS. Patients were randomised at the time of surgery if it was predicted that residual disease would be less than or equal to 1 cm in greatest diameter. Laparoscopy could be used before CRS to help make this prediction.

Hyperthermic intraperitoneal chemotherapy with cisplatin 100 mg/m^2 was administered at 40°C over 90 min by an open technique. Sodium thiosulfate was administered by a six-hour intravenous infusion to prevent nephrotoxicity. The primary outcome was progression-free survival (PFS), while the secondary outcomes were overall survival, adverse side-effects, and quality of life.

In the intention-to-treat analysis, events of disease recurrence or death occurred in 99 of 122 patients (81%) in the CRS plus HIPEC group, and in 110 of 123 patients (89%) in the CRS group. The hazard ratio (HR) for disease recurrence or death was 0.66 (95% CI 0.50–0.87, $P = 0.003$), favouring the HIPEC group. The median PFS was 14.2 months in the CRS plus HIPEC group versus 10.7 months in the CRS group. At 5 years, 50% of the patients in the CRS plus HIPEC group had died versus 62% in the CRS group (HR 0.67, 95% CI 0.48–0.94, $P = 0.02$). The median OS was 45.7 months versus 33.9 months, showing an 11.8-month survival advantage in the CRS plus HIPEC group. There was no significant difference in grade three or four adverse events between the two groups (27% vs 25%, $P = 0.76$, respectively). There was a higher rate of stoma formation in the CRS plus HIPEC group (72% vs 43%, $P = 0.04$). Despite this, the overall health-related quality of life outcomes did not differ between the two groups.

The importance of this study is that it is the best evidence to date that a single administration of HIPEC given at the time of cytoreductive surgery for ovarian cancer might achieve significant benefits in terms of survival without excess morbidity or loss of quality of life. However, there have been criticisms of the study, including a possible premature analysis of overall survival, the heterogeneity of results between study centres, and the results being applicable to only a small sub-set of patients with ovarian cancer.[43] The HIPEC arm also received an additional, high dose of cisplatin compared to the no-HIPEC arm, which in itself might explain the improved survival. In contrast to the results of this study, preliminary results from a smaller Korean RCT of HIPEC in 184 women with stage 3 and 4 ovarian cancer failed to show a significant difference in five-year survival in the HIPEC arm.[44] It is unclear how many women in this study had residual disease less than 2.5 mm, and cases of stage four disease were included. Given the importance of achieving minimal residual disease confined to the peritoneal cavity for HIPEC to be most effective, the results of the Korean trial must be analysed more thoroughly before conclusions can be drawn about the validity of the findings. More recently, a phase III RCT of HIPEC for stage 4 colorectal cancer did not show a survival benefit over systemic chemotherapy following cytoreductive surgery.[45]

There are currently a large number of RCTs being undertaken to investigate the role of HIPEC for primary and recurrent EOC, and the results of these trials are eagerly awaited. Until the results are known, it is advised that the use of HIPEC for ovarian cancer should only be undertaken within the confines of a clinical trial. There is great interest by gynaecological oncologists to

develop and participate in international and Australian-led multicentre trials of peritonectomy (or more extensive cytoreductive surgery) and HIPEC for advanced ovarian cancer. The true benefit or otherwise of HIPEC will only be elucidated through large collaborative trials, and units using HIPEC are obliged to rigorously collect and analyse their own data. It is an exciting time for ovarian cancer treatment given the potential for improved outcomes that may result following this therapy in addition to other targeted molecular therapies that are currently being investigated.

WHERE TO NOW FOR PERITONECTOMY AND HIPEC IN AUSTRALIAN CENTRES?

The future of peritonectomy and HIPEC for advanced ovarian cancer in Australia will depend not only on the results of ongoing clinical trials, but also on the degree of collaboration that can be established between gynaecological oncologists and their surgical and medical colleagues caring for patients with other types of peritoneal malignancies. The Australian and New Zealand Peritoneal Malignancy Collaboration was established in early 2017 with a membership that includes surgeons specialising in peritonectomy, colorectal and upper gastro-intestinal procedures, interested gynaecological oncologists, medical oncologists, nurses and administrative staff involved in the planning and delivery of peritonectomy services. The collaboration has an emphasis on improving the training of surgeons in peritonectomy procedures and in establishing clinical trials for peritoneal malignancies within a multidisciplinary framework. Being part of this collaboration is an ideal opportunity for gynaecological oncologists to not only share their clinical knowledge and specialised surgical skills, but to improve their own skills in the surgical management of advanced gynaecological malignancies. Furthermore, this partnership could enhance the training of gynaecological oncology fellows in advanced abdominal peritoneal and gastro-intestinal surgical procedures. There are plans underway to commence an Australian and New Zealand-centred study of peritonectomy and HIPEC for advanced ovarian cancer. Most importantly, it will be imperative that gynaecological oncologists take a leadership role in deciding which patients with ovarian cancer could benefit most from this treatment approach going into the future.

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