

Review

Surgical and systemic therapies for addressing occult disease in advanced epithelial ovarian cancer

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Abstract

The incidence of peritoneal recurrence in advanced epithelial ovarian cancer (EOC) is high and could be attributed to the high prevalence of occult disease that persists despite complete cytoreductive surgery (CRS) and systemic chemotherapy. Several therapeutic approaches have been used to address such occult disease. Hyperthermic intraperitoneal chemotherapy (HIPEC) acts on microscopic disease as well as free intraperitoneal cancer cells shed during surgery, thus, reducing the risk of recurrence. Maintenance therapies like Poly ADP-Ribosyl Polymerase (PARP) inhibitors and the anti-angiogenic agent bevacizumab are used as maintenance therapies to delay recurrence. The most definitive way to eradicate such occult disease completely is resection of the peritoneum. The high preponderance of occult disease in the parietal peritoneum and some regions of the visceral peritoneum has led some surgeons to investigate the role of a total parietal peritonectomy (TPP) performed along with wide resection of the visceral peritoneum as a strategy for addressing occult disease. The mechanism of action differs from that of HIPEC and systemic therapies. It is possible that the benefit of each of these therapies is additive. EOC is a heterogeneous disease with a number of clinicopathological and molecular factors influencing the prognosis. There are likely to be different subgroups of patients that benefit from each of these 4 therapies or a combination of these. In this manuscript, we review the rationale and current evidence for the use of each of these therapies and discuss the potential role of a TPP in light of other therapies.

Keywords: Advanced ovarian cancer; Cytoreductive surgery; Total parietal peritonectomy; HIPEC; PARP inhibitors; Anti-angiogenic therapy

1. Introduction

Advanced epithelial ovarian cancer (EOC) remains an incurable disease with high recurrence rates despite advances in locoregional and systemic therapies [1]. Most of the recurrences are in the peritoneum and the disease remains confined to the peritoneum for prolonged periods [2]. This could be attributed to the high incidence of occult disease in EOC.

Several locoregional and systemic therapeutic approaches have been used to address such occult disease [3]. Hyperthermic intraperitoneal chemotherapy (HIPEC) acts on microscopic disease as well as free intraperitoneal cancer cells shed during surgery, thus, reducing the risk of recurrence [4]. The addition of HIPEC to interval cytoreductive surgery (CRS) showed a benefit in both progression-free and overall survival over interval CRS alone. The benefit of HIPEC in addition to primary CRS is being evaluated in clinical trials [5]. Maintenance therapies like Poly ADP-Ribosyl Polymerase (PARP) inhibitors and the anti-angiogenic agent bevacizumab have the potential to delay recurrence and prolong survival [3]. These therapies act on both systemic and intraperitoneal disease. Bevacizumab has shown a survival benefit only in patients with subopti-

mal debulking surgery and those with stage IV-A disease. PARP inhibitors are recommended for patients with BRCA mutations and/or homologous recombination deficiency (HRD) following completion of first-line therapy [6].

The most definitive way to eradicate occult disease completely is resection of the peritoneum. The parietal peritoneum and some visceral peritoneal sites are more prone to harboring occult disease in patients undergoing interval CRS and visual inspection is inaccurate in predicting the presence or absence of residual disease [7]. Complete resection of the parietal peritoneum or a total parietal peritonectomy (TPP) performed along with wide resection of the visceral peritoneum could be an effective strategy for addressing this occult disease. The mechanism of action differs from that of other locoregional therapies like HIPEC and systemic therapies and thus, it is possible that the benefit of each of these therapies is additive. In this manuscript, we review the rationale and current evidence for the use of each of these therapies and discuss the potential role of a TPP in light of other therapies. The pathways of peritoneal spread and disease distribution in the peritoneal cavity, response to systemic therapy which form the basis of formulating therapeutic strategies are described and discussed.



2. Peritoneal dissemination and response to systemic chemotherapy

2.1 Patterns of spread in ovarian cancer

An understanding and knowledge of patterns of peritoneal spread is vital to the treatment of ovarian cancer. Peritoneal spread includes the mode of peritoneal dissemination and the actual distribution of disease in the peritoneal cavity. Peritoneal dissemination occurs through the transcoelomic or transmesothelial route, the translymphatic route and the haematogenous route. In the first two routes, single cells or clusters of cells are shed from the tumor spontaneously, due to surgical manipulation or spontaneous or iatrogenic rupture and gain access to the peritoneal cavity [8,9]. In transmesothelial spread, these free intraperitoneal cells attach to the peritoneum, breach the mesothelial barrier and reach the submesothelial tissue where they proliferate [10]. In translymphatic spread, the tumor cells reach the subperitoneal tissue through the lymphatic stomata. Anatomical regions in the peritoneal cavity with a high concentration of lymphatic stomata like the greater omentum, appendices epiploicae of the colon, inferior surface of the diaphragm, falciform ligament, the recto-uterine pouch and small bowel mesentery are more frequently involved compared to other sites in this pathway [11,12]. Both transmesothelial and translymphatic spread occur in EOC.

Some tumors employ the same pathways for peritoneal spread but the actual distribution of disease in the peritoneal cavity differs which could be attributed to the inherent disease biology [13]. For example, with transmesothelial spread it may be expected that the pattern of distribution in EOC is random proximal distribution, in which peritoneal spread occurs in vicinity of the tumor.

However, it has been observed that the parietal peritoneum is involved first and disease follows the pattern of redistribution [14]. Based on the information derived from experimental studies and few clinical studies, cancer spread in ovarian cancer could be best described as wide-spread cancer distribution (Fig. 1). Ascites is seen early in EOC. Pelvic ascites is staged as IC disease and causes redistribution of cancer cells. Certain sites are involved early in the course of peritoneal spread like the omentum, pelvic peritoneum, right paracolic gutter and right subphrenic peritoneum [15].

Clinical studies on the disease distribution in EOC are few and have several limitations.

In a retrospective study of 214 patients with EOC (67.7% with serous carcinoma; nearly 90% has stage III and IV disease) the pelvic peritoneum was the commonest site to be involved, followed by the colon and then the diaphragm [16]. In a prospective multi-centric study, it was shown EOC involved the lower regions (regions 5, 6 and 7 according to the description in Sugarbaker's peritoneal cancer index) first, followed by the middle regions (0, 4, 8—mainly the omentum) and then the upper regions (1, 2, 3) [14]. None of the patients had involvement of the upper re-

gions without involvement of the lower regions. The small bowel was the last site to be involved. Disease on the small bowel surface and mesentery was not seen in the absence of disease in all three regions of the peritoneal cavity. Ninety-five percent of the patients in this study had serous EOC. A more detailed evaluation of the patterns of peritoneal spread could guide surgical resection in advanced EOC.

2.2 Presence of microscopic disease in 'normal appearing' peritoneum

In early stage disease random peritoneal biopsies lead to upstaging in 18% of the patients [17]. There are very few studies looking at the incidence of occult disease in patients with advanced EOC undergoing primary CRS. Our preliminary study showed this incidence to be 50% (unpublished results). Azaïs *et al.* [18] prospectively evaluated the incidence of microscopic disease in the unresected peritoneum at the end of CRS in 26 patients with advanced, high-grade serous EOC. Biopsies were taken from 13 regions in each patient and 26.9% had occult disease in one or more regions. After mathematical analysis, the probability that microscopic disease remained after complete macroscopic CRS in patients with EOC was 98.14% [18].

In patients receiving neoadjuvant chemotherapy (NACT), the reported incidence of occult disease ranges from 13–45% [14,19]. The incidence of occult disease around tumor nodules was 46% and that in regions that show no tumor nodules was 35% in our prospective study [20]. It has been hypothesized that residual disease after NACT harbors chemotherapy resistant stem cells which if not removed increase the risk of recurrence [21]. One study showed a higher incidence of platinum resistant recurrence and a shorter progression-free survival (PFS) in patients receiving NACT [22]. Randomized trials show a similar PFS and overall survival (OS) in patients undergoing primary or interval CRS. This is despite significantly higher rates of complete gross resection (CGR) or CC-0 resections in the NACT arm. The surgical strategy is to resect only sites of residual disease after NACT which could be responsible for this lack of difference. With a higher CGR or CC-0 the survival with NACT should be longer. Following NACT, a variety of morphological changes take place in tumor nodules. Residual nodules persist or the nodules are replaced by scars or the peritoneum appears absolutely normal. This remains an assumption and till date, no study has compared the visual appearance of tumor before and after NACT. Nevertheless, the high incidence of occult disease in both scar tissue and areas of normal appearing peritoneum, supports this assumption. In another prospective multi-center study, we reported a high incidence of occult disease in 'target regions' like the falciform ligament, umbilical round ligament and the lesser omentum in patients with EOC [23]. It is the failure to address this occult disease that could be responsible for the similar survival between the primary and interval CRS

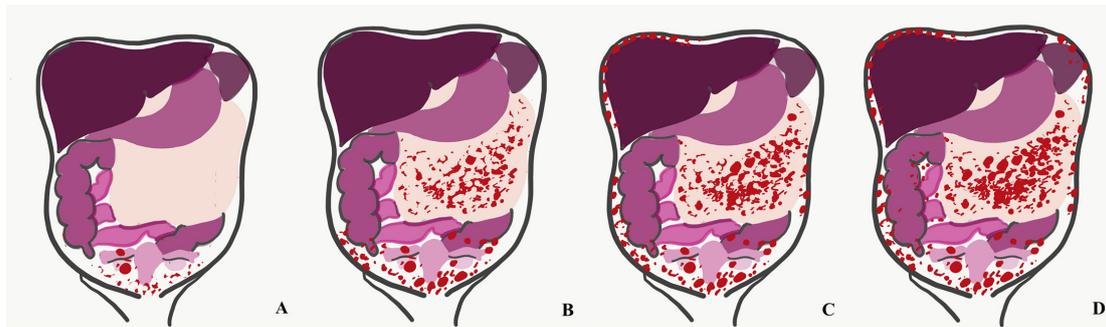


Fig. 1. The redistribution phenomenon and wide spread cancer distribution in ovarian cancer. (A) Involvement of the pelvic peritoneum that occurs early on. (B) The greater omentum and right paracolic gutter are involved next. (C) Involvement of the right hemidiaphragm seen in more advanced disease. (D) Widespread cancer distribution.

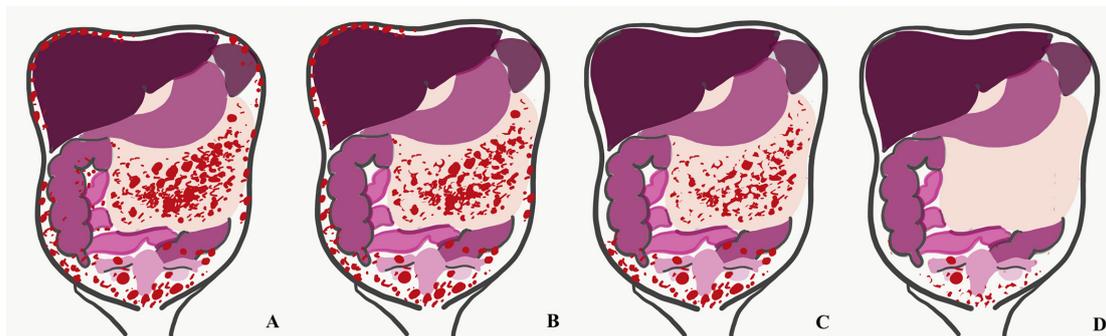


Fig. 2. Sequence of response to chemotherapy in ovarian cancer. (A) Wide spread cancer distribution. (B) The regions involved last like the small bowel mesentery and left diaphragmatic peritoneum respond early. (C) The right upper quadrant is the next area to respond. (D) The omentum, pelvis and ovaries are the last sites to respond and the most common sites of residual disease.

arms despite a significantly higher rate of CC-0 resections in the interval CRS arms in several randomized trials [24–28].

2.3 Pattern of response to neoadjuvant chemotherapy

Given the limitations of both imaging and visual inspection performed during surgery in detecting residual disease following NACT, surgical resections could be guided by the pattern of response to NACT. In our first retrospective study, we demonstrated that the response occurred in a similar sequence or pattern in 95% of the patients [29]. The small bowel mesentery was the first site to have a complete response, followed by the upper regions, the middle regions, the omentum, the lower regions and lastly the ovaries (Fig. 2). This assessment was based on the pathological evaluation of interval CRS specimens. Subsequently, our prospective study confirmed these findings [30]. In both these studies, we were not able to compare the surgical findings before, during and after NACT and it was assumed that all these regions had disease since only patients with advanced, unresectable disease were treated with NACT and interval CRS.

There are two plausible explanations for this pattern of response. First, the regions in which disease persists longer are those that are rich in lymphatics and it may be difficult

to clear the disease completely in these regions compared to those that have a paucity of lymphatics. Second, the regions involved early in course of the disease have a higher tumor burden and could harbor more clones of chemotherapy resistant cells leading to a poorer response compared to regions involved late in the course of peritoneal spread. However, only selected sites, those with the greatest probability of harboring disease were studied and the response at other sites should be studied in future studies.

2.4 Patterns of recurrence in patients with advanced epithelial ovarian cancer

When describing the patterns of recurrence, the sites of recurrence after first line therapy and the distribution of recurrent disease in the peritoneal cavity both need to be considered. The pattern of recurrence is influenced by the type of locoregional therapies used.

Seventy-five percent of recurrences in EOC occur in the peritoneum, and in almost 50% of these cases, the peritoneum is the only site of recurrence [31]. Nodal recurrence is the second most common and is usually associated with peritoneal disease [31].

A retrospective study of 104 patients showed that in comparison to patients receiving systemic chemotherapy (SC) alone, patients who received normothermic intraperi-

toneal chemotherapy were more likely to recur in the upper abdomen or in extra-abdominal nodes [32].

When HIPEC was added to interval CRS, the incidence of intraperitoneal recurrence was significantly lower than that following CRS alone [33]. In another retrospective multi-center study of 97 patients undergoing interval CRS and HIPEC, systemic sites like the lung, liver and brain were the most common sites of recurrence [34].

Disease can recur in both treated and non-treated areas of the peritoneum. In patients treated with CRS alone, pelvic recurrences are more common than upper abdominal recurrences [35,36]. In our retrospective multi-center study of 60 patients undergoing secondary CRS for recurrent disease, the upper abdomen was the most common site of recurrence (63.3%) followed by the pelvis (55%). Regional nodes were involved in nearly 50% of the patients and were a common site of occult disease [37].

Most of the recurrences from ovarian cancer are diffuse [38]. In a study of 270 patients, reported by Ferrandina *et al.* [39], ‘diffuse peritoneal carcinomatosis’ was seen in 62.1% of cases, while recurrences presented as a single lesion or multiple nodules occurred in 9.9 and 26.7% of cases, respectively. Peritoneal carcinomatosis was defined as 20 or more peritoneal nodules by Chi *et al.* [38].

3. Total parietal peritonectomy and wide resection of the visceral peritoneum

Surgical cytoreduction is the cornerstone of treatment of advanced EOC. The surgical principle which was first propounded by Hoskins was ‘to remove as much disease as possible’ and the current principle is ‘to leave behind no gross residual disease’ [40–42]. A meta-analysis published in 2002 that included 6885 patients showed a statistically significant positive correlation between percent maximal cytoreduction and the log median survival time ($p < 0.001$) [42]. Each 10% increase in maximal cytoreduction was associated with a 5.5% increase in the median survival time. Over the course of time, surgical proficiency has improved with the introduction of new surgical procedures to aid obtaining a complete cytoreduction [43,44]. Gynecological and surgical oncologists treating ovarian cancer are well-versed in performing peritonectomies and upper abdominal surgical procedures like diaphragmatic peritonectomy and resection and clearance of the superior recess of the lesser sac [45–47]. These efforts have resulted in a significant increase in the rates of complete cytoreduction or complete gross resection [44,48,49]. Though the OS has improved over time due not just to the progress in surgical therapy but also the introduction of new systemic therapies, recurrence rates remain high and the median OS is only 40–50 months (Table 1) [24–28,43].

EOC is monoclonal in origin (except low grade serous carcinoma which is polyclonal in origin), yet, widespread peritoneal involvement is common and develops early, especially in the case of high-grade serous carcinoma [50].

We hypothesize that just as a CC-0 resection has a survival benefit compared to any amount of residual disease, resecting areas prone to harboring residual disease could add to the survival benefit of a CC-0 resection.

3.1 Surgical principles and guidelines for treatment of advanced epithelial ovarian cancer

Various national and international guidelines recommend that the goal of surgery for advanced EOC should be complete gross resection or no macroscopic residual disease [51–53]. For patients in whom this is not possible, optimal debulking that is residual disease less than 1 cm in size is recommended. Residual disease less than 1 cm in size is associated with a longer OS compared to residual disease measuring more than 1 cm [51]. Peritonectomy procedures and visceral resections are performed to achieve a CGR or optimal debulking [54].

This principle is in contrast to all other solid tumors where surgical resections for early and advanced tumors are defined anatomically and not according to the size of residual disease [55]. For most solid tumors, a wide resection of the primary is performed with a minimum predefined margin (Fig. 3) [55]. This is because there is a high probability of having microscopic disease in the proximity of the tumor. Advanced epithelial ovarian cancer comprises multiple nodules scattered all over the peritoneum. There is no recommendation or consensus on the amount the peritoneum surrounding tumor nodules that should be resected. It is possible that different surgeons resect different amounts of the surrounding peritoneum that harbors occult disease. The parietal peritonectomy that is performed could be termed ‘selective parietal peritonectomy’ (SPP) in which areas bearing visible disease alone are resected.

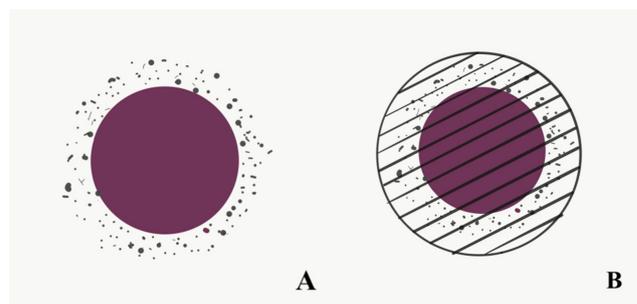


Fig. 3. Principle of surgical resection for solid malignancies. (A) Microscopic disease around tumour nodules. (B) Wide resection of tumour nodules is performed in solid tumours removing a predefined margin of normal tissue on all sides.

In both early and advanced EOC, areas of peritoneum suspicious of harboring disease are excised or biopsied [51]. ‘Suspicious’ is a very subjective term and there is no morphological description or consensus on what lesions/findings should be considered ‘suspicious’.

Table 1. Progression-free and overall-survival in patients with advanced ovarian cancer undergoing surgery and systemic chemotherapy.

First author; year [ref]	N	Trial name	Comparator arms	Optimal debulking	CC-0 or complete gross resection	Median progression-free survival	Median overall-survival
Vergote; 2010 [24]	670	EORTC 55971/NCIC OV13	PDS versus IDS	41.6% (PDS) and 80.6% (IDS)	NR	12 m in both arms	29 m (PDS) and 30 m (IDS)
Kehoe; 2015 [25]	550	CHORUS	PDS versus IDS	28% (IIC) 23% (IV)	28% (IIC) 30% (IV)	107 m (PDS) and 12 m (IDS)	22.6 m (PDS) and 24.1 m (IDS)
Fagotti; 2020 [26]	171	SCORPION-NCT01461850)	PDS versus IDS	34.2%	61.4%	15 m (PDS) and 14 m (IDS)	41 m (PDS) and 43 m (IDS)
Chi; 2011 [27]	316	Retrospective study	PDS versus IDS	24% (PDS) 54% (IDS)	71% (PDS) 86% (IDS)	13 m (IDS) and 17 m (PDS)	37 m (IDS) and 50 m (PDS)
Ru-Hain; 2012 [28]	242	Retrospective study	PDS versus IDS	NR	7.5% (PDS) and 27% (IDS)	11 m (PDS) and 14 m (IDS)	29 m (PDS) and 33 m (IDS)

Abbreviations: NR, not reported; PDS, primary debulking surgery; IDS, interval debulking surgery; m, months.

The other problem with ovarian cancer is the relatively low accuracy of all imaging modalities in determining the extent of disease accurately. Even with a peritoneal MRI for staging, the accuracy ranges between 15–70% [56,57]. Whereas imaging may be able to predict inoperability more accurately it is the inability to detect small nodules that if not looked for may be missed on surgical exploration and lead to recurrence, that is more problematic. Thus, the extent of surgery performed in advanced EOC is largely dependent on the extent of exploration performed and the surgeon's evaluation of the peritoneal lesions and it is only plausible to assume that there is a lot of variation in the extent of surgery that is performed for a similar amount or extent of disease (Fig. 4). This statement is borne out by the large differences in operative times for the same disease stages reported in different surgical studies [24–28].

3.2 Alternative surgical strategy for advanced EOC

Based on the above data, resecting visible disease alone, that is performing a selective parietal peritonectomy (SPP) especially after NACT may not be sufficient in EOC. Complete removal of the parietal peritoneum (i.e., a total parietal peritonectomy [TPP]) has shown a survival benefit in primary peritoneal serous carcinoma (PPSC) and peritoneal mesothelioma and may have a role EOC [58,59]. EOC is monoclonal in origin compared to PPSC which is polyclonal. The monoclonal origin does not support the rationale for performing a TPP [50,58,59]. The preponderance of disease in the parietal peritoneum which constitutes only 20% of the peritoneal surface area but harbours 80% of the tumour deposits is another point that favours the rationale for performing a TPP [12,17].

3.3 Total parietal peritonectomy in treatment armamentarium of advanced ovarian cancer

A total parietal peritonectomy irrespective of the extent of parietal peritoneal involvement can be performed

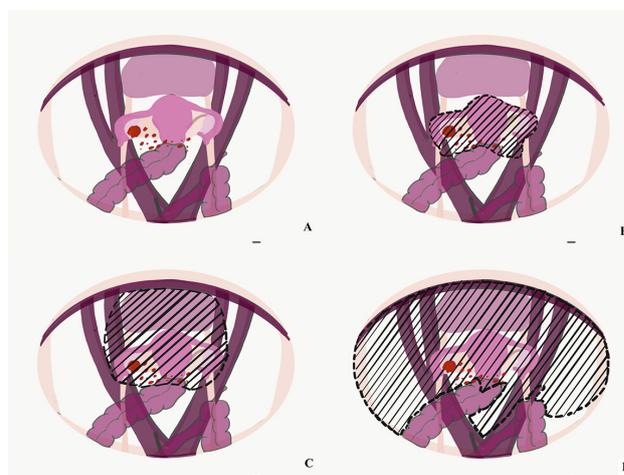


Fig. 4. Variation in the amount of peritoneum resected by different surgeons for the same amount of peritoneal disease. (A) Disease in the pelvic peritoneum. **(B)** Limited resection of the surrounding peritoneum. **(C)** More extensive peritoneal resection compared to that in B. **(D)** Complete removal of the pelvic peritoneum.

during primary or interval CRS. The peritoneum is the first line of defence and removing normal peritoneum may have its own risks [60]. However, the normal peritoneum in ovarian cancer may not be normal but ‘normal appearing’ given the high incidence of occult disease. Second, such resections are only performed in patients whom a CC-0/1 resection can be obtained.

In our retrospective multi-center study of 79 patients comparing TPP and SPP, 30 patients had a TPP. The 90-day grade 3–4 morbidity (23.3% for TPP, 14.2% for SPP, $p = 0.58$) the 90-day post-operative mortality was similar ($p = 0.58$) between the two groups [61].

The 3-year OS was 95% for TPP and 70.8% for SPP ($p = 0.06$). The only independent predictor of OS was grade

3–4 morbidity ($p = 0.01$). Microscopic residual disease was seen in 23.3% with normal looking peritoneum in TPP group. Due to the retrospective nature of this study and its heterogeneous patient population, no conclusions regarding survival benefit could be drawn. But the 3-year OS of 95% in the TPP group is an important finding [61].

We are conducting a prospective, single arm, multi-centre study evaluating the role of TPP during interval CRS. Interval CRS after NACT at the 3 centres participating in this study is only performed for patients in whom the disease is unresectable as determined on preoperative evaluation that includes a staging laparoscopy. The entire parietal peritoneum is invariably involved in these patients and thus, TPP is performed to remove the peritoneum that was involved prior to NACT. This study, the TORPEDO (total removal of the peritoneum at interval debulking for ovarian cancer) study is registered with the clinical trials registry of India (CTRI/2018/12/016789). There is a fixed surgical protocol that defines the boundaries of each peritonectomy to be performed. In addition to the parietal peritonectomies (pelvic, bilateral anteroparietal, right and left upper quadrant), a greater and lesser omentectomy is performed for all patients [20]. For mesenteric disease, resection of the involved peritoneum is performed. Complete mesenteric peritonectomy is not part of the protocol. The small bowel mesenteric peritoneum is biopsied in 4 quadrants in absence of visible disease. In addition to a TPP, wide resection of the visceral peritoneum preserving the underlying viscera whenever possible, is performed in areas prone to harbouring disease. For example, the omental attachment on the right colon and the reflection of the peritoneum from the paracolic gutter onto the mesocolon are common sites of disease and are removed (Fig. 5) [20]. Similarly, the reflection of the greater omentum on the posterior wall of the stomach that forms a boundary of the lesser sac is removed. We have a low threshold to resect the rectosigmoid colon as it is involved early in the course of disease and the probability of microscopic disease is high (Fig. 6).

As we have described previously, most of these patients do not require a diverting o'stomy and the incidence of anastomotic leaks is very low [20]. This surgery requires patient and meticulous exploration of the abdominal cavity, lysis of all adhesions, and complete mobilization of the lobes of the liver to identify all sites of residual disease and scarring. In addition to the surgical protocol there is protocol for evaluation of CRS specimens that is followed at all participating centres.

For primary CRS, the evidence is even more scarce. There is only one prospective study of 16 patients that reported the safety and feasibility of TPP during primary CRS [62]. The morbidity was higher than other reports. However, the authors did not report on the incidence of occult disease. No other prospective or retrospective study has evaluated the role of TPP in the setting of primary CRS.

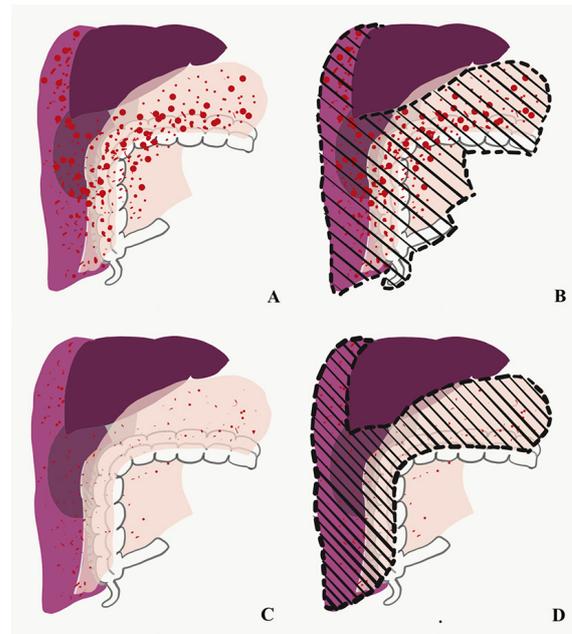


Fig. 5. Wide resection of the visceral peritoneum around the right colon. (A) Extensive involvement of the greater omentum, right paracolic gutter and right upper quadrant peritoneum. (B) A right hemicolectomy is needed to completely resect all the tumour nodules. (C) Reduction in the tumour burden following a response to chemotherapy. (D) The omental attachment on the right colon is dissected off and the peritoneum overlying the colonic mesentery resected to obtain a complete cytoreduction in the region without performing a right hemicolectomy.

3.4 Proof-of-principle for performing TPP during interval CRS

An analysis of the pathological findings in the first 50 patients enrolled in the TORPEDO study provide the proof-of-principle for performing a TPP [20]. There are two points of concern- the performance of visual inspection and the distribution of occult disease. When the parietal peritoneum alone is removed preserving a large portion of the visceral peritoneum, the accuracy of visual inspection should be lower for the parietal regions and the incidence of occult disease higher in these regions [7].

To demonstrate the accuracy of visual inspection, the surgical and pathological findings were compared in each of the 13 regions of the PCI. The sensitivity ($p = 0.103$) and specificity ($p < 0.001$) of visual inspection in detecting residual disease were significantly lower for the parietal regions (regions 0–8) compared to the small bowel regions (regions 9–12 representing the visceral peritoneum) (Table 2, Ref. [20]). The false negative were significantly higher for the parietal peritoneal regions ($p < 0.001$). When lesions scores 0–1 were considered, the sensitivity was significantly lower for the parietal regions compared to the visceral regions ($p = 0.014$) (Table 3) [20].

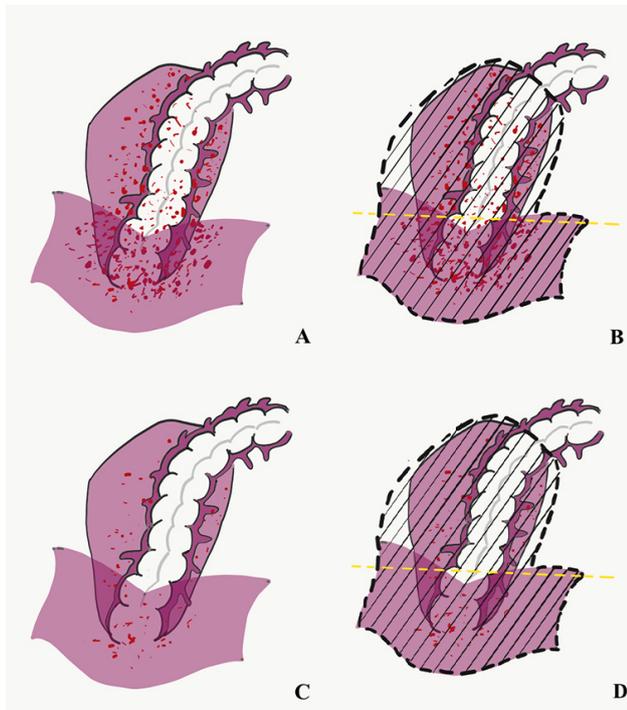


Fig. 6. Disease spread over and around the rectosigmoid in advanced ovarian cancer. (A) Extensive disease over the rectosigmoid colon. (B) Anterior resection is performed preserving the mid-rectum where the peritoneum is loosely attached and can be stripped off the rectum. (C) Reduction in the disease burden following a response to systemic chemotherapy. (D) Rectal resection is performed in the same manner as in B to clear all the disease from the recto-sigmoid mesentery.

Similarly, the incidence of both overt ($p < 0.001$) and occult ($p < 0.001$) disease was higher in the parietal regions compared to the small bowel regions representing the visceral peritoneum which supports the rationale of performing a TPP during interval CRS.

3.5 Morbidity

One major concern with performing more extensive surgery is the morbidity, its impact on the quality of life and the delay in starting adjuvant chemotherapy [20]. In the above study, 90-day grade 4–3 morbidity was 22% and the 90-day post-operative mortality 2% which could both be considered acceptable [20]. 6% required a surgical intervention for the complications. The most common complication was intra-abdominal fluid collection that required aspiration in 10% of the patients. All these patients were managed with a radiologic intervention alone performed on an out-patient basis. No bowel fistulas or perforations occurred. All patients were able to start chemotherapy within 6 weeks of surgery.

In another study of 144 patients we studied the major morbidity in patients undergoing TPP in the primary interval and recurrent settings [63]. Thirty (20.8%) patients had

primary cytoreductive surgery (CRS), 90 (62.5%) interval CRS and 24 (16.2%) CRS for recurrence. HIPEC was performed in 57 (39.5%) patients. 93.7% had all 7 peritonectomies, 61% had more than three visceral resections and 62.5% had at least one bowel anastomosis. All patients had intermediate or complex surgery according to the surgical complexity score (SCS) by Aletti *et al.* [64] 80% had a complex surgery. Grade 3–4 morbidity was seen in 31.9% and was similar with/without HIPEC. In this study a large proportion of patients had all 7 peritonectomies (93.7%) and multi-visceral resections (>3 in 61%) and this is why both the number of peritonectomies and visceral resections did not have an impact on the morbidity. On multi-variable logistic regression analysis, patients receiving NACT ($p = 0.031$) and undergoing small bowel resection ($p = 0.038$) had a higher risk of grade 3–4 morbidity and those with peritoneal cancer index (PCI) <10 ($p = 0.001$) had a lower risk. Small bowel resection was performed in 10 patients of which 9/10 had a PCI >10 and 8/10 patients had both 2 or more bowel anastomoses and resection of more than 3 viscera. Thus, small bowel resection could be considered a surrogate for more extensive surgery in this study and it was an independent predictor of an increased major morbidity. HIPEC had no impact on the morbidity. The number of bowel anastomoses (>1 in 15.2% and at least 1 in 62.3%) was not an independent predictor of increased major morbidity either. All except two patients started chemotherapy within 6 weeks of surgery. Thus, the morbidity of TPP with or without HIPEC could be considered acceptable for advanced EOC.

3.6 Impact of TPP on recurrence and survival

The impact of TPP on PFS and OS needs to be demonstrated to conclusively establish its role in the treatment of EOC during interval CRS. Our retrospective study had many limitations due to which it is not possible to derive conclusions on survival from that study [56]. There is one other retrospective study that compared outcomes in patients undergoing TPP and SPP but the study had methodological problems as the criteria for performing a TPP and SPP were not specified [65]. The data from our prospective study are not mature. We considered an important endpoint that is not usually evaluated in clinical trials—recurrence within 6 months of therapy or platinum resistant recurrence (PRR). Patients with PRR have a poorer survival and lower response rates to second line therapies. In this study of 70 patients, PRR was seen in 7.1% which represents an 80% reduction from what has been reported previously [66]. Though the most common site of recurrence was the visceral peritoneum (N = 9), seven (>40%) patients did not develop recurrence in the visceral peritoneum (Table 4, Ref. [66]). The morbidity, mortality and the incidence and distribution of occult disease were similar to our previous reports.

Table 2. Incidence of involvement of different peritoneal regions (according to Sugarbaker’s peritoneal cancer index) in absence of visible disease in 50 patients undergoing interval cytoreductive surgery (adapted from ref 20 with permission [20]).

Peritoneal region	Dissection performed	Total number in which it was involved	Incidence of occult disease*	Incidence of occult
	N (%)	N (%)	N (%)	disease in involved regions
Parietal peritoneal regions (0–8)				
0	50 (100.0)	41 (82.0)	6 (12.0)	6 (14.6)
1	50 (100.0)	33 (66.0)	1 (2.0)	1 (3.0)
2	50 (100.0)	27 (54.0)	5 (10.0)	5 (18.5)
3	50 (100.0)	22 (44.0)	2 (4.0)	2 (9.0)
4	50 (100.0)	22 (44.0)	5 (10.0)	5 (22.7)
5	50 (100.0)	31 (62.0)	1 (2.0)	1 (3.2)
6	50 (100.0)	43 (86.0)	3 (6.0)	3 (6.9)
7	50 (100.0)	31 (62.0)	2 (4.0)	2 (6.4)
8	50 (100.0)	21 (42.0)	7 (14.0)	7 (33.3)
Total no of regions	450 (100.0)	271 (60.2)	32 (7.1)	32 (11.8)
Small bowel regions (9–12)				
9	50 (100.0)	6 (12.0)	0 (0.0)	0 (0.0)
10	50 (100.0)	2 (4.0)	1 (2.0)	1 (50.0)
11	50 (100.0)	9 (18.0)	0 (0.0)	0 (0.0)
12	50 (100.0)	11 (22.0)	0 (0.0)	0 (0.0)
Total number of regions	200 (100.0)	28 (14.0)	1 (0.5)	1 (3.5)
All regions	650 (100.0)	299 (46.0)	33 (5.0)	33 (11.0)
<i>p</i> -value (for the comparison between parietal and small bowel regions)		<0.001	<0.001	0.185

*Occult disease refers to presence of disease on pathological examination when visual inspection is negative.

3.7 Impact of response to neoadjuvant chemotherapy

NACT produces a pathological complete or near-complete response in the peritoneum in around 15% of the patients [67]. In most cases, ovaries still harbour residual disease. Currently, there is no accurate method of predicting a complete response preoperatively [68]. Intraoperatively as well, it is difficult to accurately identify patients with a complete response. In other tumours, like rectal cancer, where the tumour is confined to one region of the abdominal cavity, predicting a pathological complete response is difficult and most patients require a surgical resection [69]. More number of patients and studying patterns of response in more detail with a correlation with the clinical and radiological findings is needed to see if there are subgroups in which a TPP could be omitted.

3.8 Regional lymph node involvement

Regional lymph node involvement can be secondary to the primary tumour or the peritoneal metastases [70]. Extensive pelvic peritoneal disease increases the risk of pelvic lymph node involvement. The impact of increasing tumour burden on nodal positivity has been demonstrated in one retrospective study [71]. Apart from the pelvic and para-aortic nodes, there are upper abdominal nodes like those around the porta, celiac axis, para-cardiac and sub-xiphoid nodes that can be involved secondary to peritoneal disease. Nodes in the small and large bowel mesentery can be involved secondary to bowel involvement by peritoneal deposits.

In one retrospective study, the incidence of mesorectal node involvement was correlated with the depth of rectal wall infiltration. Even in those with serosal involvement, nearly 10% had positive mesorectal nodes, and it was more than 40% in those with full-thickness involvement [71].

The LION trial does not recommend performing lymphadenectomy for ‘normal appearing’ nodes [72]. However, in our prospective study regional nodes have been a common site of failure (17.1% of all patients and 70.5% of patients with recurrence disease) [66]. When a more aggressive approach like TPP is employed, it is only prudent to be aggressive in dealing with the regional nodes as well. Whilst pelvic node dissection carries little morbidity, paraaortic lymphadenectomy carries a greater risk of complications. In our study, the main problem was post-operative fluid collections that required multiple aspirations [66]. The Careful mapping of other regional nodes that are involved secondary to peritoneal disease on imaging and during surgery should be performed and suspicious and/or metastatic nodes are resected. The extent of lymphadenectomy that should be performed with a TPP is another areas that requires evaluation in future studies.

3.9 Clinical end-points for randomized trials/prospective studies evaluating the role of TPP

TPP is a surgical therapy and it is assumed that it should provide better locoregional control. There is no consensus on what should be an ideal end-point to demonstrate the clinical benefit of locoregional therapies in EOC. Bet-

Table 3. Comparison of the performance of visual inspection in predicting the presence or absence of disease in the parietal and visceral regions in 50 patients undergoing interval cytoreductive surgery (adapted from ref 20 with permission [20]).

Parameter	Parietal regions (0–8)	Small bowel regions (9–12)	p-value	Gall bladder	Rectum	Spleen	Appendix	Right colon
	N (%)	N (%)		N (%)	N (%)	N (%)	N (%)	N (%)
Number dissected	450 (100.0)	200 (100.0)	-	50 (100.0)	35 (70.0)	23 (46.0)	18 (36.0)	8 (16.0)
False negative	32 (7.1)	2 (1.0)	0.001	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
False positive	94 (21.5)	39 (19.5)	0.685	3 (6.0)	2 (5.7)	2 (8.6)	5 (27.7)	1 (12.5)
True negative	88 (19.5)	127 (63.5)	<0.001	36 (72.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
True positive	236 (52.4)	32 (16.0)	<0.001	11 (22.0)	33 (94.3)	21 (91.4)	13 (72.3)	7 (87.5)
Sensitivity	88.0%	94.1%	0.103	100%	NA	NA	NA	NA
Specificity	48.3%	76.5%	<0.001	92.3%	NA	NA	NA	NA
Number dissected (R)	208 (46.2)	170 (85.0)	<0.001	-	-	-	-	-
False negative	26 (12.5)	2 (1.1)	<0.001	-	-	-	-	-
False positive (R)	48 (23.0)	26 (15.2)	0.144	-	-	-	-	-
True negative	88 (42.3)	127 (74.7)	<0.001	-	-	-	-	-
True positive (R)	46 (22.1)	15 (8.8)	<0.001	-	-	-	-	-
Sensitivity (R)	63.8%	88.2%	0.014	-	-	-	-	-
Specificity (R)	64.7%	83.0%	<0.001	-	-	-	-	-

Abbreviations: R, restricted value (after excluding regions with lesion scores 2 and 3); NA, not applicable.

ter loco-regional control should increase the OS especially in EOC where a delay in recurrence leads to a delay in second-line therapy, a longer platin-free interval and therefore, presumably, a better response to second-line therapies [73]. Peritoneal metastases (PM) lead to ascites and bowel obstruction and bring down the quality of life. For PM of digestive origin, it has been proposed that obstruction-free survival could be a useful end-point to demonstrate the benefit of HIPEC [74]. Our retrospective study showed that the visceral peritoneum was not a site of recurrence in 42% of the patients who developed recurrence/progression [34]. Thus, theoretically, TPP should not just prolong PFS but OS as well.

In addition to locoregional therapies, the time to recurrence is influenced by another factor that is the response to chemotherapy. Bohm *et al.* [67] demonstrated a 50% longer PFS in patients with complete or near complete response to chemotherapy compared to the moderate and poor responders. The difference in OS between the different responders was less compared to the difference in PFS between these groups. Locoregional therapies should have a greater impact on OS compared to the response to chemotherapy during first-line therapy by reducing the burden of chemotherapy resistant cells and thus enhancing the response to subsequent therapies. Thus, not just PFS but OS should be considered an important end-point while evaluating the role of TPP. A recent meta-analysis of 17 unique randomized trials of standard, consolidation, and maintenance systemic therapies or targeted therapies with data from 11029 unique patients did not establish PFS as a surrogate end point for OS in first-line treatment of advanced EOC and the authors recommended that when PFS is the primary end-point, OS should be a secondary end point [75].

4. HIPEC

4.1 Rationale and pitfalls of HIPEC

HIPEC involves the circulation of a heated chemotherapy solution in the peritoneal cavity for 30–120 minutes using a roller pump and heat exchanger (now custom made machines). The direct instillation of chemotherapy into the peritoneal cavity has many theoretical benefit like direct exposure of the tumor cells to the drug, a decreased systemic absorption which allows a prolonged exposure of the tissues to the drug and a reduced systemic absorption thus, allowing larger doses to be administered [76,77]. Intraperitoneally administered drugs can gain access to the subperitoneal lymphatics and act on trans-lymphatic tumor dissemination. Through the sub-peritoneal lymphatic network, drugs reach different areas of the subperitoneal space even when the mechanical distribution is uneven [78,79].

Despite this pharmacokinetic advantage, the depth of penetration of the chemotherapeutic drug into the peritoneum and tumor nodules is not more than 2–3 mm and HIPEC acts best in the presence of minimal or no residual disease [80,81]. HIPEC performed following a complete CRS acts on free intraperitoneal cancer cells and reduces the implantation of these cells at the surgical site [82].

There are many theoretical benefits of hyperthermia but the clinical benefit has not been proven for the treatment of PM. Heat itself is cytotoxic, it potentiates the cytotoxicity of the chemotherapeutic drugs and in some instances, helps in overcoming drug resistance [83,84].

4.2 Current evidence on the benefit of HIPEC

4.2.1 Primary CRS/debulking

Most of the preliminary evidence on HIPEC in addition to primary CRS comes from retrospective studies (the majority having less than 100 patients) which showed that

Table 4. Sites and timing of recurrence/disease progression in 17 patients* of the 70 patients undergoing interval cytoreductive surgery (adapted from ref. 66 with permission [66]).

Patient	Sites of recurrence								Time to recurrence (Months)
	Mediastinal nodes	Pleura	Infra-renal retroperitoneal nodes	Suprarenal retroperitoneal nodes	Retroperitoneal soft tissue	Visceral peritoneum	Small bowel mesentery	Parenchymal liver metastases	
1	+								12
2	+	+	+			+	+	+	12
3	+	+	+				+	+	16
4			+	+	+				11
5				+		+			15
6		+							2
7				+		+			15
8								+	9
9				+		+			3
10				+		+			12
11									13
12			+	+		+	+		6
13			+			+			13
14	+								8
15				+		+			18
16			+	+					17
17							+		3
	4	3	6	8	2	9	4	1	

*The sites involved at the first detection of recurrence/progression on imaging have been considered.

the morbidity of HIPEC in addition to CRS was acceptable [2]. The study population included patients undergoing CRS-HIPEC at different time points in the history of EOC, the time period spanned several years, and the treatment protocols even within the small groups were heterogeneous. The selection criteria were not clearly defined, and several series comprised patients with extensive disease that were referred to specialized units after having undergone unsuccessful prior surgical attempts [2].

Chiva *et al.* [85] published a systematic review that included 11 studies comprising 248 patients in which there was no benefit of adding HIPEC to primary CRS. Contrary to this, two systematic reviews and meta-analyses reported improved outcomes with HIPEC in addition to CRS. Huo *et al.* [86] performed a meta-analysis of 9 comparative and 28 non-comparative studies evaluating the role of HIPEC for primary and recurrent EOC. In the primary setting, the meta-analysis performed on patients of 3 studies showed a survival benefit with HIPEC at 2, 3, 4, 5 and 8 years. These studies included patients with Stage II–III–B as well and did not make a distinction between patients undergoing primary and interval CRS. In a subgroup analysis of patients with stage III–C and IV alone, the hazard ratio (HR) for OS was 3.61 (95% CI: 1.55–8.37; $p = 0.003$) and for OS at 5 years 2.25 (95% CI: 1.07–4.71; $p = 0.030$) both favouring the use of HIPEC [86]. Zhang *et al.* [87] performed a similar meta-analysis and demonstrated a benefit of HIPEC for all patients undergoing primary or interval CRS (HR = 0.59, 95% CI: 0.46 to 0.75 for OS and HR = 0.41, 95% CI: 0.32 to 0.54 for PFS) as well as those with stage III or IV disease

(HR = 0.64, 95% CI: 0.50 to 0.82 for OS and HR = 0.36, 95% CI: 0.20 to 0.65 for PFS).

Lei *et al.* [88] reported a retrospective propensity score-matched study including patients with EOC undergoing primary CRS with (N = 425) or without HIPEC (N = 159) [55]. HIPEC was performed with 50 mg/m² of Cisplatin on days 1, 3, and 5, which is not the common practice.

At a median follow-up of 42.2 months, the addition of HIPEC led to a nearly 16-month increase in OS (median OS, 49.8 m; 95% CI, 45.2–60.2 m for CRS-HIPEC versus 34.0 m; 95% CI, 28.9–42.3 months for CRS alone). The iterative HIPEC was associated with a 36% reduction in the risk of death [PS weighted HR, 0.64; 95% CI, 0.50–0.82; $p < 0.001$] without a significant increase in severe surgical complications and systemic toxicities. All the limitations of a randomized study and a retrospective analysis apply to this study.

In the only RCT reported so far, Lim *et al.* [89] reported no benefit of the addition of HIPEC to primary CRS. One-hundred-eighty-four patients undergoing both primary and interval CRS were randomized to HIPEC or no HIPEC. Though the trial has been completed, the final results have not been reported or published. The small sample size, the inclusion or patients undergoing both primary and interval CRS and performing HIPEC for patients with optimal debulking (residual disease < 1 cm) are some of the limitations of this trial.

There are four RCTs in progress looking at the role of HIPEC in addition to primary CRS (Table 5, Ref. [5,56]): The OVIHIPEC-2 trial in Europe, Australia and the

Table 5. Published and ongoing clinical trials on the role of HIPEC in advanced ovarian cancer.

ClinicalTrials.gov ID	Phase; primary institution/group	Indication	HIPEC regimen (s)	Control arm	Experimental arm	Main outcomes
Van Driel [5]	Phase 3 randomized controlled trial; Netherlands Cancer Institute	Advanced ovarian cancer (interval surgery)	Cisplatin 100 mg/m ² for 90 mins	CRS + SC	CRS + HIPEC + SC	Benefit in the HIPEC arm in PFS and OS; Same morbidity
Lim [56]	Phase 3 randomized controlled trial; National Cancer Centre, Korea	Advanced ovarian cancer (primary and interval surgery)	Cisplatin 75mg/m ² for 90 mins	CRS + SC (92)	CRS + HIPEC + SC (92)	No benefit of HIPEC in the PDS arm; benefit with HIPEC in PFS and OS after 20 months of follow up in the IDS arm
Only abstract; full results not available						
NCT03842982 (CHIPPI)	Randomized Phase III; Centre Oscar Lambert	Advanced ovarian, FT and PP cancer	Cisplatin 100 mg/m ² for 90 mins	PDS/IDS + SC	PDS/IDS + HIPEC + SC	
NCT02349958	Non randomized; Bay Area Gynecology Oncology, US	Advanced ovarian cancer; other primary sites	Various regimens		CRS + HIPEC + SC	
NCT02124421 (HOT trial)	Mercy Medical Center, US	Advanced ovarian cancer	Carboplatin (AUC 6) for 90 mins	CRS + SC + IPC	CRS + HIPEC + SC	
NCT01970722	City of Hope Medical Center, UC	Advanced ovarian, FT, uterine and PP cancer	Various regimens		CRS + HIPEC + SC + IPC	
NCT02567253 (OvIP1)	Quadruple arm, Phase II; University Hospital, Ghent, Belgium	Advanced ovarian cancer	Cisplatin 75 mg/m ² NT or HT for 90 mins		CRS + HIPEC + SC	
NCT01628380	Randomized, Phase III; A.O. Ospedale Papa Giovanni XXIII, Italy	Advanced ovarian cancer	Cisplatin 100 mg/m ² + paclitaxel 175 mg/m ²	CRS + SC	CRS + HIPEC + SC	
NCT02681432	Randomized, Phase III; Hospital General de la Ciudad Real, Spain	Advanced ovarian cancer	Paclitaxel 175 mg/m ² for 60 mins	CRS + SC	CRS + HIPEC + SC	

*Time not specified.

Abbreviations: SC, systemic chemotherapy; CRS, cytoreductive surgery; PDS, primary debulking surgery; IDS, interval debulking surgery; PFS, progression-free survival; OS, overall survival.

United States (NCT03772028), the CHIPPI trial in France (NCT03842982), the HIPECOC trial (NC04280185) and EHTASEOCCS trial (NCT03373058) both in China.

4.2.2 Interval CRS/debulking

The OVHIPEC-1 trial showed a benefit in both PFS and OS with the addition of HIPEC to interval CRS compared to interval CRS alone [5]. The use of HIPEC led to a reduction in the risk of death by 33% [HR: 0.67; 95% CI: 0.48–0.94; p -value = 0.02] [5]. Though the morbidity and mortality were similar in both arms, certain complications like infection and thromboembolism and the rate of stoma formation were more in the HIPEC arm. There were many criticisms of this trial [90,91]. The survival rates (PFS-10 m and OS-41 m) were similar to studies in which no HIPEC was used. This trial had a very stringent follow-up protocol and strict criteria for diagnosis of recurrence due to which the recurrences may have been reported earlier than usual. Second, since randomization was performed intraoperatively, survival was calculated from the date of surgery and not the time of starting NACT (approximately reduction of 3m in PFS and OS). The intraoperative randomization was considered improper and fraught with bias. However, HIPEC is performed only in patients with residual disease measuring less than 2.5 mm and only those patients in whom a complete CRS is feasible or has already been achieved can be randomized to evaluate the benefit of HIPEC over CRS alone. The sample size was considered small and the primary end-point that is PFS was not met with. The long recruitment period of 9 years and reduced benefit in patients recruited at the most experienced centers were other criticisms. Despite these limitations, an OS benefit of 12 m cannot be ignored and HIPEC has now been included in many national and international guidelines including the NCCN guidelines as a treatment option for patients undergoing interval CRS.

In the trial from Korea discussed in the previous section, there was a trend towards a longer PFS and OS with HIPEC in patients who had a follow up of more than two years [90]. The trial has been completed but the final results have not been disclosed or published. Ongoing clinical trial on HIPEC in addition to interval CRS are listed in Table 5.

4.3 Morbidity of HIPEC

One of the main criticisms of HIPEC has been the morbidity and the subsequent impact on starting adjuvant therapy. Published randomized trials on HIPEC and large cohort studies have shown that the morbidity of HIPEC is acceptable (Table 6, Ref. [4,63,88,92,93]. In the OVHIPEC-1, the rate of stoma formation was more in the HIPEC arm but this can be avoided by placing an additional layer of interrupted sutures around the rectal anastomosis as described by Sugarbaker [4,94]. Most of the times, the mid-rectum is preserved and this additional layer of sutures can be easily placed. The other specific toxicity is nephrotoxicity (with

the use of Cisplatin HIPEC) that can be prevented by using the appropriate dose of Cisplatin and nephroprotective drugs like sodium thiosulfate in the perioperative period [95].

In our retrospective study described previously in this manuscript, the combination of TPP and HIPEC had an acceptable morbidity at different time-points. In both the univariate and multivariate analysis, HIPEC did not have an impact on the morbidity.

5. Maintenance therapy after completion of first-line therapy

Given the high incidence of occult disease and peritoneal recurrence the benefit of maintenance cytotoxic chemotherapy has been investigated in several studies. There was no benefit in OS in any of these studies (GOG178, AGO-GINECO, MITO-1 and After-6) [91,96–98]. Contrary to this, some of the trials evaluating the role of targeted therapies have shown a clinical benefit and some of these drugs are recommended as maintenance therapy for advanced EOC [99].

6. PARP inhibitors

Poly (ADP-ribose) polymerase 1 (PARP1) is an important protein in the base excision repair (BER) pathway for DNA single strand breaks (SSBs) and double strand breaks (DSBs) as well [100]. These breaks are repaired by the homologous recombination repair (HRR) pathway in which the PARP enzymes play an important role [101]. In patients with impaired or deficient HRR like those with BRCA mutations, inhibition of PARP enzymes by PARP inhibitors (PARPi) leads to repair by non-homologous end joining (NHEJ) which leads to genomic instability and cell death. This mechanism of action of PARPi is known as synthetic lethality [102]. Homologous recombination repair deficiency (HRD) is seen in 50% of the high grade serous ovarian cancers of which about 20% are related to germline and somatic BRCA mutations and the rest to mutations in the non-BRCA HRR genes *ATM*, *ATR*, *RAD 51*, *PALB2* [103,104].

The SOLO1, a randomized, double-blind, phase III trial randomized 391 patients with stages IIIC–IV high grade serous or endometrioid ovarian cancers to either a placebo or to olaparib (300 mg twice a day) for two years or till disease progression after completion of first line chemotherapy [105]. All patients had BRCA 1 or 2 germline or somatic mutations. Median PFS from randomization, was 13.8 months in the placebo arm and was not reached in the olaparib arm (HR 0.30; 95% CI: 0.23 to 0.41, $p < 0.01$). The PFS rate at 3 years was 60% in the olaparib arm versus 27% in the placebo arm. The median PFS to the first subsequent therapy were 51.8 months in the olaparib arm and 15.1 months in the placebo arm (HR 0.30; 95% CI: 0.22 to 0.40). At the time of PFS analysis, the interim OS data were immature. Serious adverse effects were seen

Table 6. Comparison of major morbidity and mortality following CRS and HIPEC and TPP and HIPEC for EOC.

Year [ref.]	No of patients	Overall grade 3–4 morbidity	Post-operative mortality	HIPEC arm	CRS alone arm	Most common complications
2018 [4]	245	25.3%	0.4%	27%	25%	Abdominal pain, infection, ileus
2021[88]	584	23.2%	0%	28.1%	11.5%	Electrolyte imbalance, anemia, leukopenia, neutropenia
2012 [92]	566 (advanced and recurrent both)	31.3%	0.8%	-	-	Leukopenia, haemorrhage, digestive fistula
2016 [93]	226	14.1%	2.5% (for the whole cohort of 511 patients)	-	-	-
2021[63]	90	33.3%	4.4%	35.0%	29.8%	Respiratory complications, intraabdominal fluid collections, wound dehiscence; intraabdominal abscess

in 21% in the experimental arm and in 12% in the control arm. There were no treatment related deaths in either arm. In a subsequent subgroup analysis of the trial, a reduced risk of recurrence with olaparib was seen in patients undergoing primary or interval cytoreductive surgery, those with a CC-0 resection as well as those with residual disease, in patients with a complete or partial response to first line therapy at baseline and in patients with BRCA1 and BRCA 2 mutations both [106].

PRIMA/ENGOT-OV26/GOG-3012 randomized 733 women with stages I-IV ovarian cancer to the PARPi Niraparib or placebo after completion of first line chemotherapy [107]. 373 patients (50.9%) were HRD positive, including 223 BRCA mutated patients. The PFS was statistically longer in the HRD population (median PFS of 21.9 months versus 10.4 months) and in the overall population (median PFS of 13.8 months vs. 8.2 months) with an HR of respectively 0.43 (95% CI, 0.31 to 0.59, $p < 0.001$) and 0.62 (95% CI, 0.50 to 0.76, $p < 0.001$). OS data are not yet mature. In the unplanned analysis of the HRP group, there was a modest benefit of Niraparib over a placebo (median PFS of 8.1 months vs. 5.4 months; HR of 0.68 (95% CI, 0.49 to 0.94).

VELIA/GOG-3005 is a prospective randomized phase III trial that randomized 1140 patients with stages III–IV of EOC to 3 arms: Arm A-Patients received low-dose veliparib (150 mg twice daily) throughout chemotherapy followed by full dose (300 mg twice daily) in maintenance; Arm B-veliparib only in combination with chemotherapy followed by placebo maintenance; Arm C- placebo in combination with chemotherapy and during maintenance in the arm C. 298 (26%) had BRCA mutations; 329 (29%) were HRD without BRCA mutations; and 33% were HRP [108]. Veliparib in arm A was associated with an improved PFS over chemotherapy alone (arm C) but not in the concomitant veliparib arm B. The median PFS in the BRCA mutated cohort was 34.7 vs. 22 months with an HR of 0.44 (95% CI, 0.28 to 0.68, $p < 0.001$) with and without veliparib respectively, in the HRD cohort it was 31.9 vs. 20.5

months corresponding to an HR of 0.57 (95% CI, 0.43 to 0.76, $p < 0.001$) and 23.5 vs. 17.3 months in the intention to treat (ITT) cohort corresponding to an HR of 0.68 (95% CI, 0.56 to 0.83, $p < 0.001$). They were no clinically significant difference between the two arms in quality-of-life parameters.

The PAOLA-1/ENGOT-ov25 trial randomized 806 patients with stages III-IV of high grade serous and endometrioid EOC to bevacizumab and olaparib or bevacizumab and placebo after completion of first line chemotherapy [109]. Olaparib or placebo was continued for 24 months and bevacizumab for 15 months. 30% had stage IV high grade serous EOC, 60% underwent complete cytoreduction, 70% had no evidence of disease or complete response to chemotherapy and 30% had a deleterious, germline or somatic BRCA mutation. The median PFS was statistically longer in the olaparib arm compared to the placebo arm [22.1 months versus 16.6 months; HR of 0.59 (95% CI, 0.49 to 0.72, $p < 0.001$)]. In the BRCA mutated population, the median PFS was 37.2 vs. 21.7 months in favor of the combination [HR of 0.31 (95% CI, 0.20 to 0.47)] and in HRD population (including BRCA mutated patients) the median PFS was 37.2 vs. 17.7 months [HR of 0.33 (95% CI, 0.25 to 0.45)] also favoring the olaparib arm. No benefit of olaparib was seen in the HRP population. The incidence of cardio-vascular or nephrotoxic adverse events frequently observed with bevacizumab was not higher in the combination arm. No differences in health-related quality of life were observed in the 2 arms.

7. Bevacizumab

The vascular endothelial growth factor (VEGF) that promotes angiogenesis, has been linked to hematogenous spread and formation of ascites in ovarian cancer [110]. The benefit of using bevacizumab as concomitant adjuvant and maintenance therapy has been evaluated in two randomized trials. The GOG 218 trial randomized 1873 patients

with incompletely resected stage III and IV disease to the anti-VEGF agent bevacizumab administered during adjuvant chemotherapy and as maintenance therapy thereafter for 12–15 months or adjuvant chemotherapy alone [111]. The primary end-point was PFS. The median PFS was 14.1 months in bevacizumab-arm versus 10.3 months in the control arm [hazard ratio (HR) of 0.72 (95% confidence interval (CI) 0.63 to 0.82, $p < 0.001$)]. There was no benefit in OS in the ITT population. A post-hoc analysis showed a benefit in OS in patients with stage III disease and suboptimal debulking and stage IV disease [112]. The ICON 7 trial randomized 1528 patients with stage I–IV to adjuvant chemotherapy with bevacizumab followed by maintenance therapy or to adjuvant chemotherapy alone [113]. The median PFS was 19.8 months in the experimental arm versus 17.4 months in the control arm, [HR of 0.87 (95% CI 0.77 to 0.99, $p = 0.04$)]. However, OS was not significantly increased in the ITT analyses. Adverse events related to bevacizumab included hypertension, hemorrhage, thromboembolic events and gastrointestinal perforations. In both trials, the benefit in PFS benefit associated with bevacizumab was seen largely in women with sub-optimal debulking or those with stage IV disease. Patients with a CC-0 resection were not included in the GOG-218 trial and represented a minority of the population of the ICON-7 trial. Both trials only included patients undergoing primary CRS/debulking.

It was observed that the survival curves in both the bevacizumab and non-bevacizumab arms merged rapidly after the discontinuation of bevacizumab which implies that the PFS benefit was observed only during bevacizumab maintenance treatment [114]. The BOOST trial (ClinicalTrials.gov Identifier: NCT01462890) will determine if a prolonged administration of bevacizumab up to 30 months could further improve PFS.

8. Current recommendations for maintenance therapy

Currently, the overall survival data are not mature for any of the trials on PARP inhibitors. An update on the SOLO-1 trial showed a median PFS of 51 m in the olaparib arm (unpublished results). Given the marked benefit in the PFS and possibility of a reduction in PRR and ER, olaparib is recommended for maintenance therapy following completion of first-line chemotherapy for patients with BRCA mutated tumors (Table 7, Ref. [5,24–26,66,105,107,109,111,112]) [115]. There is however, no formal analysis of either of these end-points and the trials were not designed to address these questions. The role in HRD population with no BRCA mutations is less clear and it is not recommended for patients with HRP tumors. Niraparib could be used for patients irrespective of BRCA mutation status though the evidence is less robust especially for patients having a CC-0 resection [114].

Bevacizumab could be used for both HRD and HRP tumors but the evidence once again is less convincing es-

pecially for patients with a CC-0 resection. Moreover, two trials failed to show a benefit in OS except in patients with suboptimal debulking and stage IV disease and the results of the third trial are awaited. The benefit in patients with suboptimal debulking and stage IV disease is more pronounced and it may be used for these patients. The optimal duration of therapy is still under investigation [114].

The recommendation of various experts is that the use of PARP inhibitors should be guided by molecular tests for HRD and not traditional clinical factors [115].

A study on the cost effectiveness of maintenance therapies showed that none of the maintenance therapies was cost-effective when the patients had to pay for the therapy [116].

9. Combination of TPP with other locoregional and systemic therapies

The main cause of recurrence in ovarian cancer is the high burden of occult disease that is not eradicated effectively with systemic chemotherapy alone. In patients who have incomplete or suboptimal surgery, therapies other than SC are needed to eradicate this disease more effectively. TPP is a sure-shot way of addressing occult disease in the peritoneal regions that are resected. Through it, a large proportion of the occult disease is removed. However, it is likely that there is disease at some sites that is not addressed. Given the lack of evidence, it may be considered an experimental approach. HIPEC can eradicate microscopic disease but this effect is dependent at least in part on the chemosensitivity of the tumour cells and there is no objective method of assessing it. It also acts on free intraperitoneal cancer cells shed during CRS and prevents their implantation at the surgical sites. With a TPP, the residual disease in the parietal and visceral areas resected is completely removed and this represents over 80% of the areas harbouring disease in EOC. HIPEC can still eradicate disease from the peritoneum that has not been resected – the visceral peritoneum. It may thus, be assumed that the benefit of these two strategies should be additive. We performed TPP and HIPEC in combination for advanced and recurrent EOC and found the morbidity to be acceptable [63].

Similarly, PARPi and bevacizumab act on microscopic disease and systemic disease as well. PARPi have the added benefit of producing shrinkage of gross residual disease resulting in a CR. The response to PARPi is sustained compared to that obtained with bevacizumab that wears away when the drug is discontinued. EOC is a heterogeneous disease with a number of clinicopathological and molecular factors influencing the prognosis.

Thus, it is plausible that there are different subgroups of patients that benefit from each of these 4 treatment strategies or a combination of these. For example, patients who are HRP and have a poor response to SC could be the ones that benefit most from a combination of TPP and HIPEC. Clinicians often question the role of locoregional therapies

Table 7. Platinum resistant recurrence and early recurrence reported in studies and clinical trials on TPP, HIPEC, PARPi and bevacizumab maintenance therapy.

Sub-group [ref]	N	Stages included	CC0/1	Optimal debulking	Platinum resistant	Early recurrence
					recurrence	recurrence
					N (%)	N (%)
TPP prospective study (TORPEDO) [66]	70	IIIC–IVA	92.7%	100%	5 (7.1)	10 (14.2)
SOLO-1 trial Interval CRS (Olaparib arm) [105]	94	IIIC–IVA	81%	-	12 (12.7)	23 (24.4)
SOLO-1 trial CC-0 resection (Olaparib arm) [107]	200	III–IV	100%	-	23 (11.5)	33 (16.5)
SOLO-1 trial -BRCA mutations (Olaparib arm) [107]	257	III–IV	76.6%	-	31 (12.0)	56 (21.7)
PRIMA trial (Niraparib arm) [107]	487	I–IV	-	-	175 (35.9)	320 (65.7)
PAOLA-1 -BRCA mutated tumors (olaparib arm) [109]	157	III–IV	-	-	7 (3.8)	144 (8.2)
EORTC-NCIC trial NACT arm [24]	334	IIIC–IVA	45.5%	80.6%	-	179 (53.5)
CHORUS trial NACT arm [25]	274	IIIC–IVA	39%	73%	76 (27.7)	155 (56.5)
SCORPION trial (NACT arm) [26]	87	IIIC–IVA	77%	98.6%	-	24 (27.5)
OVIHIPEC-1 trial; HIPEC arm [5]	122	IIIC	69%	98%	-	55 (45.0)
ICON 7 trial (Bevacizumab arm) [111]	764	I–IV	-	74%	71 (9.2)	300 (39.2)
GOG-218 trial (Bevacizumab arm) [112]	1873	Incompletely resected stage III; any stage IV	-	>41%	64 (10.2)	237 (38.0)

Abbreviations: TPP, total peritoneal resection; HIPEC, hyperthermic intraperitoneal chemotherapy; PARPi, PARP inhibitors; NACT, neoadjuvant chemotherapy.

in patients who are BRCA mutated and receiving olaparib maintenance therapy. Resistance to PARPi is a clinical problem that is a focus of current research [117]. Locoregional therapies like TPP and HIPEC could eradicate the occult disease more effectively and reduce the incidence of resistance to PARPi [117]. Most patients treated with TPP with or without HIPEC irrespective of the molecular profile may not derive much benefit from the addition of bevacizumab especially if they also have a complete morphological and biochemical response. Similarly, HIPEC may have a limited benefit in patients who have a very good response to systemic chemotherapy.

Future research should explore the role of each of these therapies in different prognostic subgroups to identify the treatments that confer the maximum benefit.

Apart from the clinic-pathological and molecular factors, other factors like the availability of surgical expertise, technology and equipment and the morbidity/toxicity and cost of each therapy have an impact of the treatment that is offered.

10. Conclusions

Studies on peritoneal spread and response to systemic chemotherapy EOC show that the incidence of occult disease is high in the peritoneum that appears ‘normal’ during surgery and is likely to be the source of recurrent disease. TPP performed along with wide resection of the visceral peritoneum could be a more effective strategy for addressing this occult disease compared to other locoregional

therapies like HIPEC and systemic therapies. However, the other therapies have the benefit of addressing the areas that are not addressed by TPP. The morbidity of TPP as part of first-line therapy for EOC is acceptable. Further research is needed to demonstrate the impact of TPP on survival and both PFS and OS should be the end-points of studies evaluating its role. The evidence for the use of HIPEC, PARPi and bevacizumab is evolving.

Clinicopathological and molecular factors have identified different prognostic subgroups of ovarian cancer. Future research should aim to identify which therapies are most beneficial for each sub-group. Not just the PFS and OS but the morbidity/toxicity and cost-effectiveness of each treatment should be considered. The patterns of peritoneal spread and recurrence need further study as well.

Author contributions

AB—conceptualization, literature search, data collection and interpretation, analysis of data, supervision, manuscript preparation, manuscript editing, approval of the final draft. SS—conceptualization, literature search, data collection and interpretation, analysis of data, manuscript editing, approval of the final draft. PK—conceptualization, literature search, data collection and interpretation, analysis of data, manuscript preparation, manuscript editing, approval of the final draft. SM—conceptualization, literature search, data collection and interpretation, analysis of data, manuscript editing, approval of the final draft.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest.

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