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REVIEW

Intraperitoneal chemotherapy in ovarian cancer: a review of tolerance and efficacy

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Purpose: To review the two main approaches of intraperitoneal (IP) chemotherapy delivery in ovarian cancer: postoperative adjuvant IP chemotherapy after cytoreductive surgery (CRS) and intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods: A literature search was conducted to identify studies that employed postoperative adjuvant IP chemotherapy after CRS or combined CRS and intraoperative HIPEC in patients with ovarian cancer. Data of interest included chemotherapy protocol, morbidity and mortality, and survival data.

Results: Three large randomized controlled trials comprising 707 patients with advanced ovarian cancer who received postoperative adjuvant IP chemotherapy were reviewed. Morbidity rate ranged from 56% to 94% in IP chemotherapy, and mortality rate ranged from 1% to 2%. Median disease-free survival ranged from 24 to 28 months, and overall survival ranged from 49 to 66 months. Planned chemotherapy completion rates ranged from 42% to 71%. Twenty-four nonrandomized studies that reported HIPEC comprised 1167 patients with both advanced and recurrent ovarian cancer. In patients with advanced ovarian cancer, mortality ranged from 0% to 5%, minor morbidity ranged from 16% to 90%, and major morbidity ranged from 0% to 40%. Median disease-free survival ranged from 13 to 56 months, and overall survival ranged from 14 to 64 months. Survival at 5 years ranged from 35% to 70%. In patients with recurrent ovarian cancer, the mortality rate ranged from 0% to 10%, minor morbidity ranged from 7% to 90%, and major morbidity ranged from 0% to 49%. Median disease-free survival ranged from 13 to 24 months and overall survival from 23 to 49 months. Survival at 5 years ranged from 12% to 54%.

Conclusion: There is level-one evidence suggesting the benefit of postoperative adjuvant intraperitoneal chemotherapy for patients with advanced ovarian cancer after cytoreductive surgery, albeit catheter-related complications resulted after treatment discontinuation. Studies report the use of HIPEC predominantly in the setting of recurrent disease and have demonstrated encouraging results, which merits further investigation in future clinical trials.

Keywords: intraperitoneal chemotherapy, ovarian carcinoma, hyperthermic, intraoperative, cytoreductive surgery

Introduction

Ovarian cancer is the fifth leading cause of cancer death in females, with an estimated 22,280 women in the United States being diagnosed, accounting for 15,500 deaths in 2012.[1] Epithelial ovarian cancer accounts for the majority of ovarian cancers (>75%). The diagnosis is often delayed because of the nonspecific nature of its presenting symptoms, most commonly abdominal bloating and gastrointestinal disturbances. This insidious onset results in diagnosis at an advanced stage. The prevalence of advanced

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stage disease with peritoneal and distant metastasis (FIGO stage III/IV) is high, with the chance of cure low.[2] The overall 5-year survival rate of patients with ovarian cancer of all stages is 44%,[2] and it decreases to <25% in patients with advanced disease.[3]

Ovarian cancer spreads through exfoliation of malignant cells into peritoneal fluid, disseminating along the abdominal and pelvic peritoneum, resulting in peritoneal metastases. This was previously regarded as a preterminal condition.[4] Although ovarian cancer is often responsive to initial maximal cytoreductive surgery (CRS) and platinum-based chemotherapy, there remains a high rate of recurrence and poor long-term survival. Maximal cytoreductive surgical efforts against recurrent ovarian cancer have been shown to be independently associated with overall survival.[5] Intraperitoneal (IP) chemotherapy, given by infusion of chemotherapeutic agents directly into the peritoneum, has been investigated by some groups and has demonstrated an improvement in overall and disease-free survival.[6,7] Two forms of IP chemotherapy may be delivered: postoperative adjuvant IP chemotherapy delivered as adjuvant treatment after recovery from CRS, and intraperitoneal chemotherapy delivered as a heated chemoperfusate intraoperatively, known as hyperthermic intraperitoneal chemotherapy (HIPEC).[8] Adjuvant IP chemotherapy has been evaluated in several randomized trials, and HIPEC has been demonstrated to be effective in the management of peritoneal dissemination of other malignancies, including colorectal cancer,[9] pseudomyxoma peritonei,[10] and peritoneal mesothelioma.[11] A recent systematic review on the combination of CRS and HIPEC in ovarian cancer suggests potential benefits in disease-free and overall survival rates, with acceptable rates of morbidity and mortality.[12] The conclusion from this systematic analysis was limited by the heterogeneity and small sample size of available studies at the time.

This review serves to describe the tolerance and efficacy of the two approaches to IP chemotherapy delivery.

Methods

A literature search was conducted on the EMBASE, Medline, and PubMed databases using combinations of the search terms "intraperitoneal," "chemotherapy," "hyperthermic," "intraoperative," and "ovarian cancer." The search was limited to the English language and to humans. Studies that employed postoperative adjuvant IP chemotherapy after CRS or combined CRS and HIPEC in patients with ovarian cancer, published from 1995 to 2011, were selected for review.

Data of interest included the two main types of intraperitoneal chemotherapy protocol: postoperative adjuvant IP chemotherapy or intraoperative HIPEC, the definition and percentage of optimal CRS and time, minor morbidity, major morbidity, disease free, and overall and longer-term survival data. Morbidity where defined included minor morbidity where complications were resolved with medical management and where no invasive intervention was required. Major morbidity was defined as complications where urgent definitive or invasive intervention, such as surgical, ICU admission, or radiological intervention, was required.

Postoperative adjuvant intraperitoneal chemotherapy

The concept of delivering chemotherapy directly to the tumor led to the use of intraperitoneal chemotherapy in ovarian cancer. In 1978, Dedrick et al[13] reported that when ovarian tumors present on the peritoneum were exposed directly to chemotherapy drugs, it resulted in a higher intratumoral drug concentration than that achieved via the systemic route. Early clinical studies indicate that intraperitoneal chemotherapy delivery achieves a 10 to 20 times-higher tumor-chemotherapy dose than does the systemic delivery route.[14]

The support for combined postoperative intravenous (IV)/IP chemotherapy comes from eight randomized controlled trials, which were analyzed in a Cochrane review published in 2006.[7] Three large randomized controlled trials that employed IP catheter delivery of chemotherapy were identified and are included in this review.[6,15–17] The three trials included 707 patients who received IP chemotherapy; their characteristics are summarized in Table 1. All studies included only stage III ovarian cancer patients. The studies employed a combination of IV and IP chemotherapy, and this was compared to IV-only chemotherapy control arms. The common IP chemotherapy agent employed was cisplatin (100 mg/m^2) delivered every three weeks over six cycles.

Completion rates of all cycles of IP chemotherapy ranged from 42% to 71%, compared with 58%–86% in IV chemotherapy. This difference was attributed to high catheter-related complication rates, as well as to adverse hematological and gastrointestinal events. Major complications occurred in 69%–90% of IV chemotherapy patients and in 56%–94% of IP chemotherapy patients. Minor morbidity was not recorded. Mortality rates were similar, ranging from 1% to 2% in the IP group and from 0% to 2% in the IV group. Median disease-free survival in the IP chemotherapy patients ranged from 24 to 28 months, which was superior to the IV chemotherapy patients, whose median disease-free survival

Table 1 Intraperitoneal chemotherapy delivery via catheter – key studies

Authors	n	IP/control	Chemotherapy used	Morbidity and mortality			Survival	
				Completion (%)	Mortality (%)	Morbidity major (%)	Median DF survival (months)	Median overall survival (months)
Armstrong et al[6]	205	IP	IV paclitaxel 135 mg/m^2 over 24 h (day 1) + IP cisplatin 100 mg/m^2 (day 2) + IP paclitaxel 60 mg/m^2 (day 8)	42	2	94	24	66
	210	Control	IV paclitaxel 135 mg/m^2 over 24 h (day 1) + IV cisplatin 75 mg/m^2 (day 2)	83	2	90	18	50
Markman et al[15]	235	IP	IV carboplatin for two courses every 28 days, followed 4 weeks later by IV paclitaxel 135 mg/m^2 over 24 hours (day 1) + IP cisplatin 100 mg/m^2 (day 2)	71	1	80	28	63
	227	Control	IV paclitaxel 135 mg/m^2 over 24 hours (day 1) + IV cisplatin 75 mg/m^2 (day 2)	86	1	78	22	52
Alberts et al[16]	267	IP	IV cyclophosphamide (600 mg/m^2) + IP cisplatin (100 mg/m^2)	58	1	56	nr	49
	279	Control	IV cyclophosphamide (600 mg/m^2) + IV cisplatin (100 mg/m^2)	58	0	69	nr	41

Abbreviations: DF, disease-free; IP, intraperitoneal; nr, not recorded.

ranged between 11 and 22 months. This superior disease-free survival translated into overall survival gains, with the IP chemotherapy group and the IV chemotherapy group having a median overall survival of 49–66 and 41–52 months, respectively. Longer-term survival data at 3 and 5 years were not recorded. GOG-172 showed the longest median survival (65.6 months in the IP group) of all phase 3 GOG trials in advanced ovarian cancer.[6]

Intraperitoneal catheters are commonly implanted on the anterior abdominal wall after ovarian cancer cytoreduction or after full recovery from the initial surgery, and after thorough discussion and counseling about the potential benefits of this route of chemotherapy administration. IP chemotherapy delivery is selected for use in patients, following optimal cytoreduction. Although the recommended candidate is one who has not undergone a bowel resection, this is regarded as a relative contraindication, as this procedure should not be a limiting factor in precluding one's ability to achieve complete cytoreduction and subsequently receive this route of chemotherapy administration. IP chemotherapy may commence during the immediate early postoperative period, or once a patient recovers fully from ileus and has regained normal bowel function. Earlier administration may theoretically allow enhanced chemotherapy penetration into residual tumor nodules prior to the formation of the adhesions that often prevent free circulation of peritoneal chemoperfusate.

Despite the evidence from meta-analyses of randomized controlled trials demonstrating that IP chemotherapy achieves superior disease-free, overall survival, one of the factors limiting its widespread adoption is the associated toxicity, as demonstrated by the most recent randomized trial, GOG-172,[6] where only 42% of patients in the IP arm completed their planned six cycles of IP chemotherapy. Walker et al[17] examined the IP catheter outcomes in this trial. Of the 119 patients who did not complete the treatment, 16 patients (13%) did not receive any IP chemotherapy, 68 patients (57%) received one to two cycles of IP chemotherapy, and 35 patients (29%) received three to five cycles of IP chemotherapy. In this group of patients, 40 of 119 patients (34%) discontinued IP chemotherapy due to catheter-related problems, 45 patients (38%) discontinued because of poor tolerance of the IP treatment, and 34 patients (29%) discontinued because of chemotherapy complications or disease progression.[17] This high rate of catheter and route-of-delivery issues raises doubts over the tolerability of IP chemotherapy; consequently, this approach has not become routine clinical practice despite the availability of level 1 evidence supporting its use.

Hyperthermic intraperitoneal chemotherapy (HIPEC)

Hyperthermic intraperitoneal chemotherapy (HIPEC) was first described by Spratt et al[18] in the treatment of peritoneal tumor from pseudomyxoma in 1980. The rationale of combining heat with intraperitoneal chemotherapy is the added benefit of the synergistic effect of heat and cytotoxic drugs.[19] Furthermore, this technique is delivered intraoperatively after cytoreduction, and this allows full peritoneal chemoperfusate circulation, with the timing of its administration to occur prior to the formation of adhesions that might limit peritoneal fluid circulation. This technique also avoids the need for implantation of peritoneal access devices, hence reducing catheter-related complications such as infection, and hence negating the issues of tolerance.[20]

Numerous nonrandomized comparative and observational studies employing a combination of CRS and HIPEC for ovarian cancer have been published. We identified 24 studies comprising 1167 patients.[21–44] Eleven studies have previously been reviewed by our group, which we published as a systematic review encompassing 895 patients. The present review includes new data from an additional 418 patients.[21–31] We attempted to separate the disease timepoint of HIPEC treatment, as the majority of these studies report treating patients with both advanced and recurrent ovarian cancer without properly accounting for other contributing factors, such as platinum sensitivity and chemoresistance (Table 2). There are subtle variations in each institution's HIPEC protocol. The most common chemotherapy agent was cisplatin, which was used in 18 of the studies, either as monotherapy or in combination with mitomycin or doxorubicin. The median intra-abdominal temperature was 42°C, with a range of 37°C–45°C. The median duration of infusion was 90 minutes, with a range of 60–120 minutes. One study did not report its HIPEC protocol.[26] The median duration of CRS and HIPEC was 480 minutes, with a range of 330–620 minutes. The majority of studies employed the definition of optimal cytoreduction as 0 or <0.25 cm, (range of 0 cm to <2 cm). Optimal cytoreduction was achieved in 66.3% of patients (range 19%–100%) (Table 3).

Fifteen studies reported data on 584 patients with advanced ovarian cancer undergoing HIPEC treatment. Collectively, these studies reported a perioperative mortality ranging from 0% to 5%. Minor morbidity ranged from 16% to 90%, and major morbidity ranged from 0% to 40%, although only two studies had a major morbidity of >20%.[29,31] The median average of disease-free survival ranged from 13 to 56 months, and median overall survival from 24 to 64 months. Survival at 3 years was 48%–60%, and at 5 years was 35%–70%.

Table 2 HIPEC studies for ovarian cancer and patient background

Authors	Level of evidence	n	Disease status	Chemoresistance	Previous chemo
Tentes et al[21]	Class III	43	Advanced and recurrent	Yes	Yes
Königsrainer et al[22]	Class III	31	Recurrent	Yes	Yes
Fagotti et al[23]	Class III	41	Recurrent	No	Yes
Cascales Campos et al[24]	Class III	46	Advanced and recurrent	nr	Yes
Parson et al[25]	Class III	51	Advanced	nr	Yes
Spiliotis et al[26]	Class II	24	Recurrent	nr	nr
Deraco et al[27]	Class III	26	Advanced	No	No
Roviello et al[28]	Class III	53	Advanced and recurrent	nr	Yes
Pomel et al[29]	Class III	31	Advanced	Yes	Yes
Celeen et al[30]	Class III	42	Recurrent	Yes	Yes
Lim et al[31]	Class III	30	Advanced	nr	Yes
Bereder et al[32]	Class III	246	Advanced and recurrent	Yes	Yes
Pavlov et al[33]	Class III	56	Advanced and recurrent	nr	Yes
Guardiola et al[34]	Class III	47	Advanced	nr	Yes
Di Giorgio et al[35]	Class II	47	Advanced and recurrent	nr	Yes
Bae et al[36]	Class II	67	Advanced	No	Yes
Cottee et al[37]	Class III	81	Recurrent	Yes	Yes
Raspagliesi et al[38]	Class III	40	Recurrent	Yes	Yes
Gori et al[39]	Class III	29	Advanced	nr	Yes
Look et al[40]	Class III	28	Advanced	nr	Yes (18), no (10)
Ryu et al[41]	Class II	57	Advanced	No	Yes
Zanon et al[42]	Class III	30	Recurrent	nr	Yes
Chatzigeorgiou et al[43]	Class III	20	Recurrent	Yes	Yes
Cavaliere et al[44]	Class III	20	Recurrent	Yes	Yes

Abbreviation: nr, not recorded.

Table 3 Hyperthermic intraperitoneal chemotherapy and cytoreductive surgery protocol

Authors	HIPEC protocol			CRS protocol		
	HIPEC drug/dose	Temp	Duration	Median CRS + HIPEC duration (min)	Definition optimal CRS (cm)	Optimal CRS [n(%)]
Tentes et al[21]	Cisplatin 50 mg/m^2 and doxorubicin 15 mg/m^2 or gemcitabine 1000 mg/m^2	42.5–43	60–90	nr	0	30 (70)
Königsrainer et al[22]	Cisplatin 50 mg/m^2	42	90	593	<0.25	28 (90)
Fagotti et al[23]	Oxaliplatin 460 mg/m^2	41.5	30	330	<0.25	41 (100)
Cascales Campos et al[24]	Paclitaxel 60 mg/m^2 or cisplatin 75 mg/m^2	42–43	60	440	<0.25	38 (83)
Parson et al[25]	Carboplatin 1000 mg, mitomycin 30 mg (median values)	40–42	60–120	480	0	20 (40)
Spiliotis et al[26]	nr	nr	nr	nr	nr	nr
Deraco et al[27]	Cisplatin 40 mg/L and doxorubicin 15 mg/L	42.5	90	620	0	15 (58)
Roviello et al[28]	Cisplatin 100 mg/mq and mitomycin C 25 mg/mq	41–43	60	480	0	12 (23)
Pomel et al[29]	Oxaliplatin 350 or 460 mg/m^2	42–44	30	nr	≤1	9 (29)
Celeen et al[30]	Cisplatin 100–250 mg/m^2 or oxaliplatin 460 mg/m^2	40.5–41	30[c]/90[c]	498	0	21 (50)
Lim et al[31]	Cisplatin 75 mg/m^2	41.5	90	576	<0.25	29 (97)
Bereder et al[32]	Cisplatin, cisplatin and doxorubicin, cisplatin and mitomycin C	42	90	nr	0	nr
Pavlov et al[33]	Doxorubicin 0.1 mg/kg/day, max 10 mg/day and cisplatin 15 mg/m^2, max 30 mg/day	40	120	399	<0.25	52 (93)
Guardiola et al[34]	Cisplatin 90 mg/m^2	37	120	430	≤1	27 (57)
Di Giorgio et al[35]	Cisplatin 75 mg/m^2	42–43	60	528[a]	<0.25	41 (86)
Bae et al[36]	Paclitaxel 175 mg/m^2 or carboplatin 350 mg/m^2	43–44	90	nr	<1	48 (72)
Cottee et al[37]	Cisplatinum at 20 mg/m^2/L	44–46	90	348[a]	<0.25	45 (56)
Raspagliesi et al[38]	Cisplatin 25 mg/m^2/L and mitomycin C 3.3 mg/m^2/L and cisplatin 43 mg/L and doxorubicin 15.25 mg/L	42.5	nr	410[a]	0	33 (83)
Gori et al[39]	Cisplatin 100 mg/m^2	41–43	60	nr	<2	6 (19)
Look et al[40]	Cisplatin and doxorubicin or mitomycin C and 5FU	nr	90	nr	<0.25	16 (57)
Ryu et al[41]	Carboplatin 350 mg/m^2 and interferon-a 5,000,000 IU/m^2	43–44	90	nr	<1	48 (84)
Zanon et al[42]	Cisplatin 100–150 mg/m^2	41.5	60	410[a]	<0.25	22 (77)
Chatzigeorgiou et al[43]	Cisplatin 50–75 mg/m^2	39–40	120	nr	<1.5	nr
Cavaliere et al[44]	Mitomycin C 3.3 mg/m^2/L and cisplatin 25 mg/m^2/L	41.5–42.5	90	690[a]	<0.25	nr

Notes: [a]Oxaliplatin; [b]cisplatin; [c]mean value.

Abbreviation: nr, not recorded; HIPEC, hyperthermic intraperitoneal chemotherpy; CRS, cytoreductive surgery.

For patients with recurrent ovarian cancer, 13 studies included 583 patients. The perioperative mortality ranged from 0% to 10%. Minor morbidity ranged from 7% to 90%, and major morbidity ranged from 0% to 49%. Median disease-free survival ranged from 13 to 24 months, and median overall survival from 23 to 49 months. Survival at 3 years was 35%–60%, and at 5 years was 12%–54%.

Discussion

The high rate of recurrence of ovarian cancer within the peritoneal cavity and the limited role of IV chemotherapy compared to intraperitoneal chemotherapy delivery after cytoreduction supports the role of intraperitoneal chemotherapy in achieving locoregional control within the peritoneum in ovarian cancer. There is a theoretical advantage in the delivery of high-concentration chemotherapeutic agents that act directly and eliminate residual microscopic disease, thereby achieving a pharmacokinetic profile of attaining a high drug concentration that enhances drug-tumor penetration.

The studies included in this review highlight the body of evidence supporting the advantages of intraperitoneal delivery of chemotherapy in combination with cytoreductive surgery in patients with advanced ovarian cancer. There is level 1 evidence that demonstrates the benefits of adjuvant postoperative IP chemotherapy in improving disease-free and overall survival. However, poor treatment tolerance has been the major inhibitor of the routine use of IP chemotherapy.[45] The lack of uptake of IP chemotherapy into routine clinical practice, despite the published results of three major randomized trials,[6,15,16] may also be a result of the different type of intraperitoneal chemotherapy (cisplatin), compared to the intravenous chemotherapy (carboplatin) that is being used. The 2004 International Gynecologic Cancer Intergroup Ovarian Cancer Consensus Conference[45] recommends the use of intravenous carboplatin AUC 5–7.5 and paclitaxel – 175 mg/m^2/3 hours given every 3 weeks for six cycles – as the standard of care in patients with advanced ovarian cancer.[45] This recommendation follows from evidence for improved toxicity and tolerability profiles of chemotherapy combinations of carboplatin and paclitaxel over combinations containing cisplatin[46,47] and cyclophosphamide.[48] Further, Aletti et al[49] attempted to translate research data from these randomized trials into routine clinical practice in accordance with best-practice evidence. However, in their single institution study, the investigators encountered challenges similar to those present in GOG-172, namely, the poor tolerability of IP chemotherapy that resulted only in 36% of patients completing the planned treatment. Their reasons for discontinuing treatment included catheter-related complications (38%), nephrotoxicity (14%), and sepsis (14%).[49] Hence, although potential survival benefits may be obtained with IP chemotherapy, the morbidity of IP complications, the inability to complete planned treatment, and the possible effect on survival outcomes of unknown implications of not being able to complete treatment have limited clinicians' willingness to embrace IP chemotherapy as the standard chemotherapy delivery route.

Similar data also exists from nonrandomized studies of HIPEC; however, for this treatment to be considered for future routine practice, further commitment to sufficiently powered and well-designed randomized controlled trials is essential.[50,51]

The Cochrane review of IP chemotherapy in women undergoing treatment for initial management of advanced ovarian cancer demonstrated a 21% decrease in the risk of death (HR 0.79, 95% CI 0.70–0.90) in the patients undergoing combined IV/IP therapy, versus those undergoing IV therapy alone.[7] The review of the literature regarding HIPEC (summarized in Tables 4 and 5) shows the median disease-free survival was 13–74 months in advanced, and 13–24 months in recurrent, ovarian cancer, in the studies reviewed. This compares favorably to IV chemotherapy delivered to platinum-sensitive disease (9–14 months)[52,53] and platinum-resistant disease (13 months).[54] We also found high 3-year and 5-year survival rates in both advanced and recurrent ovarian cancer. Fives studies demonstrated > 50% survival at 5 years, in advanced cancer. The promising improvement in survival outcomes may be related to the development of high-volume specialized institutions.[55]

The optimal choice of chemotherapeutic agent in HIPEC is unclear and is probably based on extrapolation of evidence from the efficacy of intravenous chemotherapy. Theoretically, the selected agent should be water-soluble, and have a low peritoneal clearance, high peritoneal concentration, high systemic clearance, and enhanced penetration and cytotoxic ability with hyperthermic application. The majority of HIPEC studies on ovarian cancer have used IP cisplatin,[21,22,24,27,28,30–35,37–40,42–44] as the HIPEC agent. Other studies included in this review employed doxorubicin,[21,27,32,33,38,40] mitomycin C,[24,28,32,38,40,44] oxaliplatin,[23,29,30] paclitaxel,[24,36] and gemcitabine.[21]

The adoption of both postoperative adjuvant IP chemotherapy and HIPEC into routine practice is potentially limited by concerns over tolerability and morbidity. Cytoreductive surgery and HIPEC for advanced (0%–5%) and recurrent

Table 4 Advanced ovarian cancer – morbidity, mortality and survival outcomes

Authors	n	Morbidity and mortality			Survival			
		Peri-op mortality (%)	Minor morbidity (%)	Major morbidity (%)	Median DF survival (months)	Median overall survival (months)	3-year survival (%)	5-year survival (%)
Tentes et al[21]	23 of 43	5	49	19	nr	37[a]	nr	54
Cascales Campos et al[24]	35 of 46	0	22	15	nr	nr	nr	nr
Parson et al[25]	51	0	nr	nr	nr	29	48	28
Deraco et al[27]	26	4	16	20	30	nr	nr	61
Roviello et al[28]	45	nr	nr	nr	nr	nr	nr	57
Pomel et al[29]	31	nr	nr	29	nr	nr	27[b]	nr
Lim et al[31]	30	0	90	40	nr	nr	nr	nr
Bereder et al[32]	62 of 246	0	nr	12	13	49	60	35
Pavlov et al[33]	31	nr	nr	nr	nr	34	nr	nr
Guardiola et al[34]	47	0	nr	13	14	nr	63[b]	nr
Di Giorgio et al[35]	22	nr	nr	nr	26	27	nr	nr
Bae et al[36]	67	0	27	0	56	nr	nr	66
Gori et al[39]	29	nr	nr	nr	54[a]	64	nr	nr
Look et al[40]	28	0	nr	11	17	46	nr	nr
Ryu et al[41]	57	4	19	4	26	61	nr	54

Notes: [a]Mean value; [b]2-year survival.
Abbreviation: nr, not recorded; DF, disease free.

Table 5 Recurrent ovarian cancer – morbidity, mortality and survival outcomes

Authors	n	Morbidity and mortality			Survival			
		Peri-op mortality (%)	Minor morbidity (%)	Major morbidity (%)	Median DF survival (months)	Median overall survival (months)	3-year survival (%)	5-year survival (%)
Tentes et al[21]	20 of 43	5	49	19	nr	37[a]	nr	54
Königsrainer et al[22]	31	0	nr	nr	nr	nr	nr	nr
Fagotti et al[23]	41	0	nr	49	24	38	92[b]	nr
Spiliotis et al[26]	24	nr	nr	nr	nr	19	50	nr
Bereder et al[32]	184 of 246	0	nr	12	13	49	60	35
Celeen et al[30]	42	0	43	7	13	37	nr	41
Pavlov et al[33]	25	nr	nr	nr	nr	40	nr	nr
Di Giorgio et al[35]	25	nr	nr	nr	16	23	nr	nr
Cottee et al[37]	81	3	7	7	19	28	nr	nr
Raspagliesi et al[38]	40	0	20	nr	24[a]	41[a]	nr	15
Zanon et al[42]	30	3	30	14	17	28	35	12
Chatzigeorgiou et al[43]	20	10	90	0	21	nr	nr	nr
Cavaliere et al[44]	20	nr	nr	nr	nr	25	50[c]	nr

Notes: [a]Mean value; [b]estimated survival; [c]2-year survival.
Abbreviation: nr, not recorded; DF, disease free.

(0%–10%) ovarian cancer mortality rates were consistent with previous high-volume tertiary institutional evidence and similar to mortality rates of other major gastrointestinal surgery.[55] Although mortality rates for HIPEC for advanced ovarian cancer were slightly higher than rates in the postoperative adjuvant IP chemotherapy treatment cohort (0%–2%) for which only the complications arising from the six cycles of treatment have been reported, it is important to take into consideration that the high complication rate reported for CRS HIPEC combines the complication rates from both the surgical and chemotherapy components of the treatment. The higher morbidity and mortality observed with recurrent disease may be related to patients having previously undergone radical surgery to achieve complete primary cytoreduction, as recommended by a recent Cochrane review.[56] Perhaps the promising combination of CRS and HIPEC in the primary setting of advanced ovarian cancer should be explored further.

The postoperative adjuvant IP chemotherapy completion rate was as low as 42% in GOG-172.[6] Catheter-related complications were the primary reason for discontinuation in 34% of patients.[17] This suggests the catheter choice and timing of insertion requires further investigation. Survival benefits were achieved despite low rates of treatment completion, which suggests adjuvant IP chemotherapy still had a significant role.

Adjuvant postoperative IP chemotherapy in the three randomized controlled trials was employed in primary advanced stage III ovarian cancer only in conjunction with optimal CRS debulking. The effect of IP chemotherapy in stage IV and recurrent disease where optimal CRS might not necessarily be achieved is under investigation.[57] The role of other chemotherapeutic agents beyond cisplatin is also being explored by current trials.[58]

The potential benefits of HIPEC compared to postoperative IP chemotherapy relate to the theoretical advantages of its synergistic hyperthermic effect on chemotherapy, to its delivery of chemotherapy to peritoneal surfaces before the development of adhesions, and to the potential it creates for avoiding postoperative catheter-related complications and subsequently improving the ability to effectively deliver intraperitoneal chemotherapy. These advantages, combined with the evidence from observational and nonrandomized data, provide a strong rationale for undertaking further clinical trial investigations in this area. However, our review of the data regarding HIPEC also highlights the significant incidence of morbidity associated with the treatment, with major morbidity ranging from 0% to 40% (only two studies had a major morbidity rate of >20%). In one study, 40% of patients required invasive medical intervention, but reported no surgical or intensive-care unit intervention.[31] Another study was discontinued due to high rates of major morbidity, with 29% of patients requiring reoperation for intra-abdominal bleeding.[29] This was the only study that employed oxaliplatin as the sole chemotherapeutic agent. The increased rates of bleeding might have been due to the greater hematological toxicity of oxaliplatin, as compared with other chemotherapeutic agents, as demonstrated in its use in colorectal and appendiceal tumors.[59]

Current evidence establishes the role of postoperative IP chemotherapy in the adjuvant setting, in patients with advanced ovarian cancer who have undergone optimal cytoreductive surgery. Yet it leaves questions unanswered with regard to the optimal IP chemotherapy regimen in terms of tolerability, the role of HIPEC, and the role of IP chemotherapy in the setting of recurrence. Despite evidence suggesting the efficacy of CRS and HIPEC in patients with both advanced and recurrent ovarian cancer, the nonrandomized nature of the data and its heterogeneity (both in terms of patient selection and treatment protocols) make it difficult to make direct comparisons with randomized data from trials of postoperative adjuvant IP chemotherapy. This difficulty again highlights the need for further prospective randomized trials to identify the potential role of HIPEC in ovarian cancer. Such trials would establish whether HIPEC presents an acceptable alternative to current standards of care for the adjuvant treatment of advanced ovarian cancer, including postoperative IP chemotherapy, and whether IP chemotherapy offers a new dimension to the multimodality approach in managing recurrent ovarian cancer.

Disclosure

The authors report no conflicts of interest in this work.

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