Review Article on Ovarian Malignancy

Intraperitoneal chemotherapy for ovarian cancer with peritoneal metastases, systematic review of the literature and focused personal experience

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Abstract: Epithelial ovarian cancer (EOC) causes 60% of ovarian cancer cases and is the fourth most common cause of death from cancer in women. The standard of care for EOC includes a combination of surgery followed by intravenous chemotherapy. Intraperitoneal (IP) chemotherapy (CT) has been introduced into the therapeutic algorithm of EOC with positive results. To explore existing results regarding intraperitoneal chemotherapy a systematic review of the literature and an analysis of our own institutional prospective database of patients treated with cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy (HIPEC) for EOC at different stages were conducted. The focused report concerning our personal experience with advanced EOC treated with cytoreductive surgery and HIPEC produced the following results: In 57 patients cisplatin + paclitaxel as HIPEC was the only significant factor improving overall survival (OS) at multivariate analysis (OR 6.54, 95% CI: 1.24–34.47, P=0.027). Patients treated with HIPEC cisplatin + paclitaxel showed a median OS of 46 months (SD 6.4, 95% CI: 33.4–58.6), while patients treated with other HIPEC regimens showed a median OS of 12 months (SD 3.1, 95% CI: 6.0–18.0). The 2y-OS was 72% and 3y-OS was 68% for cisplatin + paclitaxel as HIPEC, while the 2y- and 3y-OS was 0% for other HIPEC regimens. Patients treated with HIPEC cisplatin + paclitaxel showed a median disease-free survival (DFS) of 13 months (SD 1.6, 95% CI: 9.9–16.1), while patients treated with other HIPEC regimens showed a median DFS of 8 months (SD 3.1, 95% CI: 1.9–14.1). In conclusion, HIPEC cisplatin + paclitaxel in ovarian cancer showed positive results that may be considered semi-definitive according to the level of evidence and should be considered a starting point for further investigations. At present HIPEC cisplatin + paclitaxel should be proposed to patients with advanced ovarian cancer as standard treatment at almost all stages of disease. Platinum + taxane-based intraperitoneal regimens demonstrated superior results compared to other regimens.

Keywords: Ovarian; cancer; chemotherapy; intraperitoneal chemotherapy; upfront surgery; consolidation surgery; surgery for recurrence; salvage surgery; cisplatin; paclitaxel

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Introduction

Epithelial ovarian cancer (EOC) causes 60% of ovarian cancer cases and is the fourth most common cause of death from cancer in women. The most frequent histologic type (70% of cases) is high-grade serous ovarian cancer with a typical biological behavior. According to FIGO classification the stage III includes a tumor with involvement of one or both ovaries and/or the Fallopian tubes with peritoneal involvement, outside the pelvis (FIGO IIIb) and retroperitoneal lymph node involvement (FIGO IIIc) (1). Stages IIIb and IIIc comprise about 60% of EOC. The standard of care for EOC includes a surgical removal of all visible evidence of disease by extensive cytoreductive surgery (CRS). This includes hysterectomy and bilateral salpingo-oophorectomy, total omentectomy, appendectomy (in mucinous histologic types), removal of bulky pelvic and aortic lymph nodes, and removal of all macroscopic disease. The cancer resection is followed by intravenous (IV) chemotherapy (CT), including a platinum-based drug with or without a taxane (2,3).

Recurrence is a common event in high grade EOC, with 75% of women experiencing relapse within 2 years from diagnosis and subsequent treatment (4). Among patients with recurrent disease, two-third have peritoneal metastases (5). The most investigated factors predicting outcome after recurrence is the platinum-free interval following primary platinum-based chemotherapy and the presence of BRCA mutations (6). Traditionally, most patients with recurrent-EOC (rEOC) are treated with chemotherapy alone, the type of which is guided by the platinum sensitivity. Patients with recurrence more than six months after a complete response are considered "platinum-sensitive" (platinum-S) and can be re-treated with platinum-based CT. Patients with persistent disease after front-line treatment or patients who recur within 6 months are considered "platinum-resistant" (platinum-R) and are unlikely to respond to further platinum. In recent decades several studies concerning the role of intraperitoneal antibodies, immunotherapy, radiotherapy and the administration of chemotherapeutic agents directly into the peritoneal cavity before, during or after surgery, have been performed to evaluate their impact on survival.

Intraperitoneal (IP) CT has been introduced into the therapeutic algorithm of EOC with positive but not definitive results. Several methodologies for delivering IP CT have been described. The most common way to perform intraperitoneal chemotherapy is the hyperthermic intraperitoneal chemotherapy (HIPEC). Early post-operative intraperitoneal chemotherapy (EPIC) and the pressurized intraperitoneal aerosolized chemotherapy (PIPAC) have also been described and utilized with interesting results.

EOC HIPEC may be used with variable timing: Primary CRS, secondary CRS, interval debulking, CRS for progressive ovarian cancer, CRS in recurrent EOC and palliative surgery (2).

Our systematic review aims to present the different results of IP CT at different timepoints of the disease and to review the drugs administered intraperitoneally. Moreover, a personal experience describing new results obtained with combined administration of platinum and taxanes as HIPEC will be presented. We present the following article in accordance with the PRISMA 2009 Checklist (available at http://dx.doi.org/10.21037/jgo-2020-06).

Material and methods

Systematic review

A computerized search was performed in selected databanks (MEDLINE, Scopus, EMBASE). Citations were included for the period between January 1990 and January 2020 using the primary search strategy: ovarian cancer, intraperitoneal chemotherapy, HIPEC, EPIC, PIPAC, IP, drugs, pharmacokinetic, pharmacodynamic, hyperthermia, outcome, follow-up, consolidative, combined with and/or. No search restrictions were imposed. The dates were selected to allow comprehensive published abstracts of clinical trials, consensus conferences, comparative studies, congresses, guidelines, government publications, multicenter studies, systematic reviews, meta-analysis, large case series, original articles, and randomized controlled trials. Only EOC (serous, mucinous, clear cell, carcinosarcoma, endometrioid, cystadenocarcinoma, adenocarcinoma, Fallopian tube carcinoma, and primary peritoneal malignancies) were included in the study. The research strategy is summarized in *Figure 1*. Two reviewers (FC and PF) analyzed the literature and selected studies. Were uncertainty arises a thirs reviewer was asked to express his opinion (LA).

Personal experience:

From our electronic database we selected patients with EOC treated with CRS combined with HIPEC at different

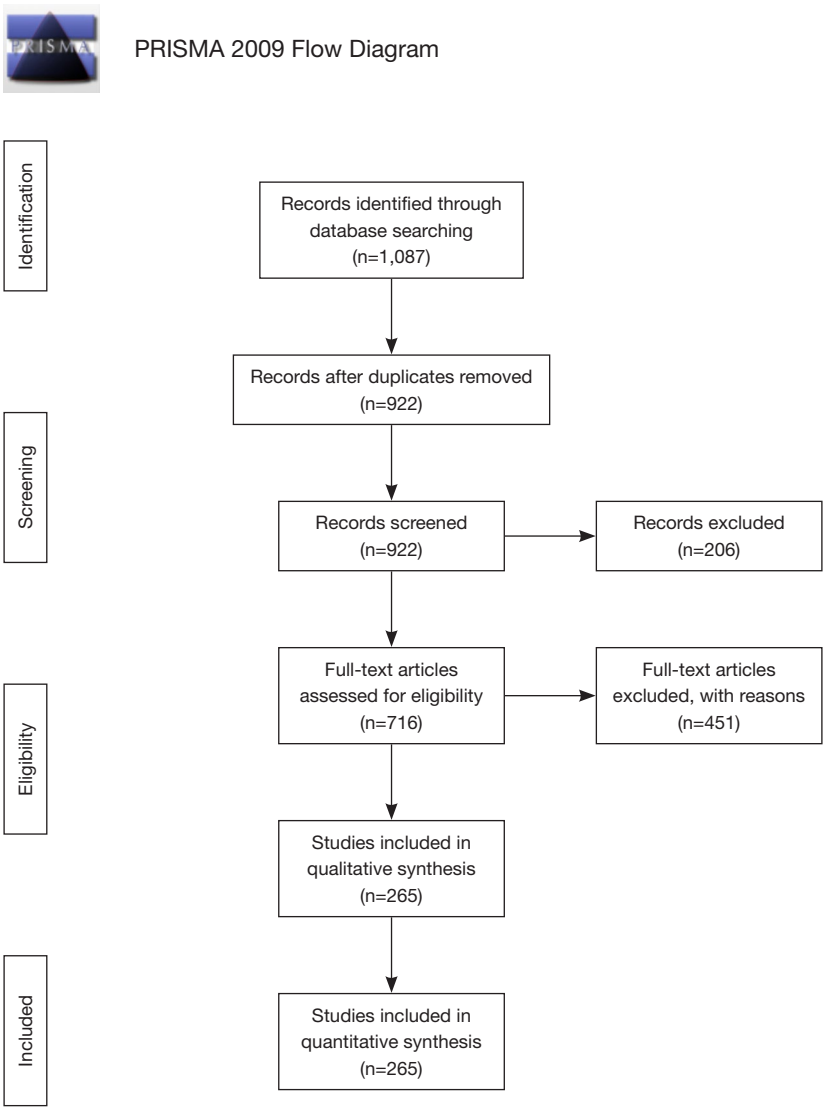

Figure 1 PRISMA flow chart.

time points of the disease (upfront CRS and HIPEC, interval CRS and HIPEC, CRS and HIPEC for recurrent EOC) from January 2011 to May 2019. A retrospective analysis of prospectively collected data was performed. All patients had an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, stage IIIC and IV EOC with resectable disease, no extra-abdominal disease and no significant comorbidities which would preclude the combined treatment. Patients with histology other than EOC and without complete data concerning follow-up were excluded.

The extent of the disease after laparotomy was determined by PCI. The abdomen and pelvis were divided into 13 regions and the size of the lesion was scored as 0–3. The maximum score was 39. CRS was performed removing all peritoneum and visceral organs involved by the tumor. Omentectomy, appendectomy and cholecystectomy were routinely performed. The completeness of cytoreduction score (CC) was estimated by the surgeon at the conclusion of the procedure according to the following classification: CC0—complete cytoreduction of all visible disease; CC1—minimal residual disease with nodules less than 2.5 cm; CC2—residual disease with nodules of 2.5 mm to 2.5 cm; and CC3—residual disease with nodules greater than 2.5 cm.

HIPEC was performed with the "coliseum technique": one inflow and four outflow catheters were placed with the open abdomen that was partially closed with a surgical adhesive drape performing a "closed-HIPEC with open abdomen technique", with a IP temperature was 42–43 ℃. HIPEC regimens were: Cisplatin 100 mg/m^2 + paclitaxel 175 mg/m^2 or cisplatin 100 mg/m^2 + mitomycin C 16 mg/m^2 or cisplatin 100 mg/m^2 + doxorubicin 15.2 mg/L of perfusate or cisplatin 100 mg/m^2 alone. After HIPEC, the perfusate was drained and the reconstruction was performed.

The primary endpoints of the analysis were DFS and OS. Univariate and multivariate analysis were performed to define factors affecting OS and DFS, as secondary endpoint.

Statistical analysis

DFS and OS were calculated as the interval between the date of CRS and HIPEC and the data of the last follow-up or of the death or of the recurrence of disease. DFS and OS were calculated with Kaplan-Meier method, and survival estimates were compared using the log-rank test. Multivariate analysis was performed for OS and DFS with Cox regression. Statistical significance was defined as a P value <0.005. All analysis was performed using SPSS 20 (IBM Corp, Released 2011, IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY, USA)

Systematic review results

The focus of the majority of the studies concerning advanced ovarian cancer are tumor biology and behavior of the tumor. Noteworthy, women with mutations of BRCA1 and BRCA2 genes have a higher risk (11–40%) to develop EOC. Cytoreductive surgery (CRS) has been showed as one of the most important factors influencing survival rates. The aim of CRS is to remove all visible disease, giving a demonstrated survival benefit with increasing completeness of cytoreduction. Intraperitoneal chemotherapy aims to remove residual microscopic disease with an additional positive effect of reducing systemic toxicity as compared to the intravenous CT.

In 2002, a meta-analysis by Bristow *et al.* analyzed 6,885 women with stage III and IV EOC. They demonstrated that if CRS removed less than 25% of the disease patients experienced a mean weighted median survival of 22.7 months. IF CRS removed more than 75% of the disease the mean weighted median survival was 33.9 months. Each 10% increase in cytoreduction rate was associated with an increase of 5.5% in median survival time (7). However, at primary surgery, in 74% and 73% respectively of women with stage III and stage IV of disease there was lymph node positivity. For this reason, IV CT remains fundamental to reduce or limit lymphatic tumor dissemination and to downstage and downsize the tumor (2,8). Despite aggressive treatment more than 60% of women had recurrence within 12–18 months. In general, recurrence is seen in 29.4% in abdominal cavity and 25.9% in the pelvis, 7.1% in retroperitoneal lymph node and 6.3% in superficial lymph nodes (9). The addition of HIPEC has many goals: To treat microscopical disease, to increase drug penetration into the tissues, to have an intrinsic antitumor effect and to increase the cytotoxicity of some CT drugs. In the open technique it can be manual and uniformly distributed (3,10).

In 2006 a National Cancer Institute (NCI) clinical announcement about EOC (FIGO III–IV) reported that adding IP CT to IV CT significantly improves survival by 12 months (range 0–16 months) if associated with optimal CRS (CC0-1). However in a recent report, Vergote *et al.* (8) suggested that IP CT was not a standard of care in first-line treatment for advanced EOC because of the results of the GOG 252 study.

Some reports comparing IP/IV to only IV therapy, showed a possible increasing in toxicity in IP/IV regimens; however, it is short-term and manageable (3). Certain CT agents, including cisplatin and paclitaxel, were found to have distinct pharmacokinetic advantages when administered intraperitoneally (11-13). The American Society of Peritoneal Surface Malignancies (ASPSM) suggests the use of mitomycin-C or paclitaxel especially in platinum-resistant disease (3).

Primary epithelial ovarian cancer

Few trials were published about HIPEC in primary EOC (pEOC). HIPEC for pEOC can be proposed in an upfront setting (U-HIPEC) or as an interval treatment (I-HIPEC) (14). U-HIPEC for primary CRS would be followed by platinum-based adjuvant chemotherapy. However, frequently women with pEOC cannot tolerate primary CRS due to a lack of fitness for major surgery or the extent of disease. In these cases a neoadjuvant chemotherapy followed by CRS plus I-HIPEC may be appropriate.

Three randomized controlled trials (RCT) have been conducted to evaluate HIPEC in upfront or interval setting in pEOC (*Table 1*). Van Driel in 2018 published the results

Table 1 Randomized controlled trials focus on intraperitoneal chemotherapy for primary EOC and recurrent EOC

First authors (ref.)	Year	Type of study	Primitive/ Recurrence	FIGO stage	IP therapy technique	no. of pts	Chemotherapy regimen	PI-Sensitive pts	CC0-1 n (%)	OS (months) [5y-OS%]	DFS or PFS (months)	Morbidity (3-4 grade/severe) %	Mortality %
Koole (15)	2019	RCT	pEOC	III	HIPEC	122	NACT (3 cycles carbo + taxol) + I-CRS+HIPEC (Cis 100 mg/m^2) + ACT (3 cycles carbo + taxol)	–	R1: 82 (67), R2a: 24 (20), R2b: 14 (11)	No significant differences in health-related QoL outcomes			
						123	NACT (3 cycles carbo + taxol) + I-CRS alone + ACT (3 cycles carbo + taxol)	–	R1: 84 (69), R2a: 22 (18), R2b: 13 (11)				
Van Driel (16)	2018	RCT	pEOC	III	HIPEC	118	NACT (3 cycles carbo + taxol) + I-CRS+HIPEC (Cis 100 mg/m^2) + ACT (3 cycles carbo + taxol)	–	R1: 84 (69), R2a: 22 (18), R2b: 13 (11)	mOS 45.7	RFS 14.2	32 (27)	0 (0)
						122	NACT (3 cycles carbo + taxol) + I-CRS alone + ACT (3 cycles carbo + taxol)	–	R1: 82 (67), R2a: 24 (20), R2b: 14 (11)	mOS 33.9 (P=0.02)	RFS 10.7 (P=0.02)	30 (25) (P=NS)	1 (0.8)
Lim (17)	2017	RCT	pEOC	III–IVV	HIPEC	92	U-CRS+HIPEC (Cis 75 mg/m^2)	–	–	NR [49.4%]	[5y-PFS 16%]	NA (67.4) anemia, NA (15.2) increase creatinine	0 (0)
						92	U-CRS alone	–	–	NR [51%] (P=NS)	[5y-PFS 20.9%] (P=NS)	NA (50) anemia, NA (4.3) increase creatinine (P=0.025 and 0.026)	0 (0)

Table 1 (*continued*)

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First authors (ref.)	Year	Type of study	Primitive/ Recurrence	FIGO stage	IP therapy technique	no. of pts	Chemotherapy regimen	PI-Sensitive pts	CC0-1 n (%)	OS (months) [5y-OS%]	DFS or PFS (months)	Morbidity (3-4 grade/severe) %	Mortality %
Spiliotis (18)	2015	RCT	rEOC	IIIC-IV	HIPEC	60	CRS+HIPEC (Cis 100 mg/m^2 +Paclitaxel 175 mg/m^2 for platinum-S) or (Doxo 35 mg/m^2 + Paclitaxel 175 mg/m^2 or MMC 15 mg/m^2 for platinum-R)	PI-S: 38 (63.3), PI-R: 22 (36.7)	CC-0: 39 (65), CC-1: 12 (20), CC-2: 9 (15)	mOS 26.7 Stage IIIC: 26.9, Stage IV: 26.4; PI-S: 26.8, PI-R: 26.6; CC-0: 30.9, CC-1: 23.9, CC-2: 12.1	–	–	–
						60	CRS + post-op IV CT	PI-S: 36 (60), PI-R: 24 (40)	CC-0: 33 (55), CC-1: 20 (33.3), CC-2: 7 (11.7)	mOS: 13.4 ($p<0.006$); Stage IIIC: 14.2; Stage IV: 11.9; PI-S: 15.2, PI-R: 10.2; CC-0: 16.1, CC-1: 11, CC-2: 6.7	–	–	–

PI-R, platinum-resistant; PI-S, platinum-sensitive; Cis, Cisplatin; Doxo, Doxorubicin; MMC, Mitomycin C; Oxa, Oxaliplatin; Carbo, Carboplatin; mOS, median overall survival; rEOC, recurrent EOC; pEOC, primary EOC; NR, not reported; NA, not available; IV, intravenous; CT, chemotherapy; NACT, neoadjuvant chemotherapy; ACT, adjuvant chemotherapy; U-, upfront; I-, interval; NS, not significant; PF, progression-free survival; RFS, recurrence-free survival; DFS, disease-free survival.

Table 2 Prospective observational studies focus on intraperitoneal chemotherapy for primary EOC

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO	IP therapy technique	No. of pts	Chemotherapy regimen	CC0-1 n (%)	OS (months) [5y-OS%]	DFS or PFS° (months)	Morbidity (3-4 grade/severe) %	Mortality %
Mikkelsen (21)	2019	Cohort	pEOC	IIa-III-IV	HIPEC	14	U-CRS+HIPEC (carboplatin 800 mg/m^2)	25 (100)[§]	NA	NA	44	0
						11	NACT+I-CRS+HIPEC (carboplatin 800 mg/m^2)					
Paris (22)	2018	Cohort	pEOC	IIIb-IV	HIPEC	40	U-CRS+ HIPEC (cisplatin 75 mg/m^2), ADJ with bevacizumab	40 (100)[§]	NA	NA	20	0
D'Hondt (23)	2016	Cohort	pEOC	IIIc	HIPEC	19	U-CRS+HIPEC (cisplatin 50 mg/m^2) + ADJ 6 cycles (carbo/taxol)	18 (94.7)	NA [2y-OS 92.3%]	33.2°	3131.2	0
							NACT 3 cycles + I-CRS + HIPEC (cisplatin 50 mg/m^2) + ADJ 3 cycles (carbo/taxol)					

pEOC, primary EOC; NA, not available; U, upfront; I, interval; NR, not reached; NACT, neoadjuvant chemotherapy; ADJ, adjuvant chemotherapy; [§], only CC0; pts, patients.

of the OVHIPEC trial (16). 245 patients were randomized to HIPEC and CRS or CRS alone in an interval setting. In the study group a 12 months increase in overall survival (OS) and 4 months increase in progression-free survival (PFS) were demonstrated. Moreover, morbidity and quality of life were similar in the two groups. Survival in the control group (33.9 months) was very similar to the results reported by Chiva *et al.* in their meta-analysis concerning primary or interval CRS alone in EOC (33 months). As a comparison I-HIPEC increased median OS to 45.7 months (versus 33.9) without increasing toxicity rate and with a similar quality of life (15,19).

Lim *et al.*, in their RCT in 2017, reported the randomization of 184 patients with similar result both in OS, PFS and mortality in an upfront setting. They reported an increased anemia and acute kidney injury rate in the HIPEC group. However, these authors found in neo-adjuvant chemotherapy (NACT) subgroup an improved outcome in favour of HIPEC and suggested that a longer follow-up may help in showing the real effect of HIPEC (20).

The last study from Koole *et al.* reported in 2019 results derived from the randomization of 246 patients managed in an interval setting. They did not find significant differences in survival, recurrence or quality of life results (15).

Observational studies reported in literature considered both primary EOC (pEOC) and recurrent EOC (rEOC).

There are three prospective studies analyzing pEOC treated with CRS + HIPEC in an upfront setting (21-23) (*Table 2*). In more than 94% of patients a complete cytoreduction (CC0) was achieved. No mortality was reported, and major morbidity ranged between 20% to 44%. Despite the different drug regimens (Paris *et al.* added adjuvant bevacizumab) the 2-year OS was 93.2% (23).

The HYPERO study (20) reported in U-HIPEC setting a mean OS of 41.7 months, with a 2y-OS of 57% and a 5y-OS of 33.3%, and in I-HIPEC setting a mean OS of 68.6 months, with a 2y-OS of 80.4% and a 5y-OS of 50.2%.

There are four retrospective studies focused on pEOC. In these studies different HIPEC timings and CT regimens were compared (up-front, interval, or associate with dose-dense chemotherapy) (24-27) (*Table 3*). CC0 was achieved in more than 73% of patients. These studies reported a mortality rate lower than 3% and a morbidity rate of 13–26.5%. The reported DFS ranged between 10 and 35 months. 5-years OS ranged between 31.5 and 46.8%. Biacchi *et al.* (25), analyzed women with primary advanced tubo-ovarian high-grade serous cancer. They

Table 3 Retrospective observational studies focus on intraperitoneal chemotherapy for primary EOC

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO	IP therapy technique	No. of pts	Chemotherapy regimen	CC0-1 n (%)	OS (months) [5y-OS%]	DFS or PFS° (months)	Morbidity (3-4 grade/severe) %	Mortality %
Rettenmaier (24)	2020	Ca-Co	pEOC	Ic-IV	HIPEC	64	DD (paclitaxel + carboplatin) + HIPEC (carboplatin) group	58 (90.6)	46.8	34.9	NA	NA
						81	I-CRS+ADJ Intraperitoneal (paclitaxel) group	76 (93.8)	46.2	34		
						100	DD CT (paclitaxel + carboplatin) + CRS group	79 (79)	41.6	27.6		
Biacchi (25)	2019	Ca-Co	pHGSC	IIIc-IVb	HIPEC	34	U-CRS+HIPEC (cisplatin 75 mg/m^2)	106 (73.6) overall	NR	29.5°	22.9	2.1
						110	NACT (3 cycles carboplatin + paclitaxel) + I-CRS+HIPEC (cisplatin 75 mg/m^2)					
							-partial response		51.5	19.5°		
							-stable response		31.5	10.5°		
							-complete response		NR	NR		
Antonio (26)	2019	cohort	pEOC	IIIc	HIPEC	19	U-CRS+HIPEC (paclitaxel)	49 (100)	123 (in subgroup with CC0, PCI<14)	95 (in subgroup with CC0, PCI<14)	26.5	0
Cascales-Campos (27)	2016	Ca-Co	EOC	IIIc-IV	HIPEC	60	U- or I-CRS: CRS+HIPEC (paclitaxel 60 mg/m^2)	45 (74%) §	NA [3y-OS 76%]	27	13	0
						51	U- or I-CRS: CRS+HIPEC (cisplatin 75 mg/m^2)			33	12	4

DD, dose-dense; Ca-Co, case-control; pHGSC, primary advanced tubo-ovarian high-grade serous cancer; pEOC, primary EOC; NA, not available; U-, upfront; I-, interval; NR, not reached; NACT, neoadjuvant chemotherapy; ADJ, adjuvant chemotherapy; §, only CC0; CT, chemotherapy; pts, patients.

showed no difference between U- or I-HIPEC in terms of DFS and OS. U-HIPEC showed similar outcome to patients who underwent I-HIPEC with complete response after NACT. However, the small number of patients undergoing U-HIPEC and the retrospective design limited the reliability of this study. No differences in terms of complications, were reported comparing HIPEC (I- or U-) with cisplatin (75 mg/m^2) or paclitaxel (60 mg/m^2) (26). Rettenmaier *et al.* (24) suggested that dose density chemotherapy with HIPEC may offer better results in terms of OS and DFS, especially in BRCA mutated patients. In conclusion, as suggested by van Driel, the optimal timepoint may be the I-HIPEC. The NACT provides a higher rate of CC0 cytoreduction and can be advantageously associated with HIPEC. Moreover, HIPEC may have a role in reducing peritoneal recurrence in EOC, which has a greater impact on survival than lymph nodal recurrence (28). The role of bevacizumab in front-line setting combined with HIPEC remains to be explored. Lastly, more attention should be paid to the genotypes in evaluating results and approaches. Futher answers might come from from the several ongoing trials (*Table 4*).

Recurrent epithelial ovarian cancer (rEOC)

The prognosis of rEOC treated with standard chemotherapy is poor, with a reported median survival of 12–24 months (29). In a few studies focusing on platinum-S patients, the median OS reaches 35 months, while in platinum-R patients it is about 12 months (22). The need for alternative treatment modalities has been pointed out by Stathopoulos *et al.*, who stated that multiple chemotherapy lines do not offer a survival benefit as compared to one or two lines (2,30).

In recent years, patients with rEOC with a BRCA mutation (BRCAmut) are most likely to benefit from treatment with PARP inhibitors, after response to a platinum-based chemotherapy, with reported DFS of 11.2 months (compared to 4.3 months of the placebo group) and OS of 34.9 months (31). For patients with wild-type BRCA (BRCAwt) treated with Olaparib, the reported DFS was 7.4 (compared to 5.5 months in the placebo group) and the median OS of 24.5 months.

The role of CRS in rEOC and its role in relation with the patients' BRCA status has recently been clarified by the AGO DESKTOP III/ENGOT ov20 trial results (32). The study showed a significant survival advantage of 7.2 months in platinum-S women with positive AGO score who underwent complete resection. They showed a DFS of 14 months without and of 19.6 months with CRS. BRCAmut patients had the best DFS regardless of having received secondary CRS or not, with a 5-year DFS of 73% in non-resected women versus 78% in resected women (P=0.558). Conversely, BRCAwt patients who underwent complete CRS had a significantly longer DFS compared with BRCAwt patients who did not receive surgery (5-year DFS of 54% *vs.* 42%; P=0.048).

HIPEC with recurrent epithelial ovarian cancer

Many retrospective and prospective observational studies (*Tables 5-8*) focused on the effects of HIPEC on patients with rEOC with heterogenous results. In these studies taken together, the reported median OS for rEOC treated with CRS and HIPEC ranges from 24.3 to 58.3 months (5y-OS: 8–79%) and the median DFS from 6 to 28 months (5y-DFS: 7–30%). In the largest study by Bakrin *et al.* (75), on 477 rEOC treated with CRS+HIPEC, the median OS was 45.7 months, with a OS of CC-0 patients of 52 months (compared to 33 months in not completely cytoreduced patients), without difference between platinum-S and platinum-R patients. In the study by Classe *et al.* (41) on 314 patients the 5y-OS was 38.0% (median OS 42 months for platinum-S and 51 months for platinum-R, P=0.38) and 5y-DFS was 14% (median DFS 13 months for platinum-S and 14 months for platinum-R, P=0.013). In the study by Bakrin *et al.* (36) on 246 patients the median OS was 48.9 months (48 months in platinum-R and 52 months in platinum-S) and the 5y-OS 35%; the median DFS was 12.8 months and the 5y-DFS 9%. Focusing on platinum-S patients treated with CRS+HIPEC, the reported OS ranged from 26 to 58.8 months (5y-OS: 50–79%) and the DFS from 6 to 27 (5y-DFS: 30%). The reported OS for platinum-R patients ranges from 9 to 51 months (33). Bakrin *et al.* (36) and Chatzigeorgiou *et al.* (39) compared OS of platinum-R and platinum-S patients with rEOC treated with CRS + HIPEC without showing significant difference.

Three case-control studies (33,56,59), all focusing on platinum-S patients, compared patients with rEOC treated with CRS+HIPEC with patients treated with traditional systemic CT. In the study by Safra *et al.* (59) and by Marocco *et al.* (56) patients treated with CRS and HIPEC showed significantly longer OS and DFS. In the study by Amira *et al.* (33) there was no significant difference in outcomes of the two groups. Safra *et al.* (59) compared BRCAmut and BRCAwt patients with rEOC treated with

Table 4 Ongoing randomized controlled trials about CRS and HIPEC for primary and recurrent EOC found in clinicalregister.gov at March 2020

Clinical trial number	Title of trial	Type of tumor	Trial design	Country	Primary/ Recurrence	State of trial
NCT02681432	Hyperthermic Intraperitoneal Chemotherapy with Paclitaxel in Advanced Ovarian Cancer (HIPECOVA)	EOC	HIPEC-arm: CRS+HIPEC with paclitaxel (175 mg /m^2) for 60 minutes at a 42–43° degrees; followed by adjuvant systemic IV chemotherapy with carboplatin (AUC=6) and paclitaxel (175 mg/m^2) for 6 cycles Control arm: CRS followed by adjuvant systemic IV chemotherapy with carboplatin (AUC=6) and paclitaxel (175 mg/m^2) for 6 cycles	Spain	P	Recruiting
NCT03842982	Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Ovarian Cancer (CHIPPI)	EOC	Experimental: Primary Debulking Surgery (PDS) or Interval Debulking Surgery (IDS) + Neo or Adjuvant chemotherapy (standard care) + HIPEC Control arm: Surgery (Primary Debulking Surgery (PDS) or Interval Debulking Surgery (IDS)) + Neo or Adjuvant chemotherapy ONLY (standard care, without HIPEC)	France	P	Recruiting
NCT03373058	Efficacy of HIPEC in the Treatment of Advanced-Stage Epithelial Ovarian Cancer After Cytoreductive Surgery (EHTASEOCCS)	EOC, FTC, PPC	Experimental arm: CRS+HIPEC with Docetaxel 75 mg/m^2 and cisplatin 75 mg/m^2 intraperitoneally in succession, followed by 6 cycles of adjuvant chemotherapy: paclitaxel 175 mg/m^2 IV>3 hour (Docetaxel 75 mg/m^2, if paclitaxel is not available) + carboplatin AUC = 5-6 IV>1 hour, every 3 weeks Control arm: CRS followed by 6 cycles of adjuvant chemotherapy: paclitaxel 175 mg/m^2 IV>3 hour (Docetaxel 75 mg/m^2, if paclitaxel is not available) + carboplatin AUC = 5-6 IV>1 hour, every 3 weeks	China	P	Recruiting
NCT03275194	HIPEC in Ovarian Carcinoma Clinical Stage IIIC and IV During Interval Laparotomy	EOC	After CRS patients will be randomized Experimental arm: HIPEC procedure with cisplatin and doxorubicin Control arm: not additional treatment	Mexico	P	Recruiting
NCT02124421	HOT: HIPEC in Ovarian Cancer as Initial Treatment	EOC, FTC, PPC	Experimental arm: CRS/HIPEC using carboplatin for 90 minutes with adjuvant IV chemotherapy with carboplatin and paclitaxel (Carboplatin AUC 6, Paclitaxel 175mg/m2) will be given every 21 days for a total of 6 cycles Control arm: CRS alone with adjuvant IV chemotherapy with carboplatin and paclitaxel (Carboplatin AUC 6, Paclitaxel 175 mg/m^2) will be given every 21 days for a total of 6 cycles	USA	P	Recruiting

Table 4 (*continued*)

Table 4 (*continued*)

Clinical trial number	Title of trial	Type of tumor	Trial design	Country	Primary/ Recurrence	State of trial
NCT03188432	Hyperthermic Intraperitoneal Chemotherapy or Intraperitoneal Chemotherapy in Comparing Quality of Life in Patients with Stage IIIC-IV Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	EOC, FTC, PPC	Experimental: Arm I (paclitaxel, carboplatin, CRS, IP chemotherapy) Patients receive paclitaxel IV over 60 minutes on days 1, 8, and 15 and carboplatin IV over 30-60 minutes on day 1. Treatment repeats every 21 days for up to 3 courses in the absence of disease progression or unacceptable toxicity. Beginning 4-8 weeks after 3 courses of chemotherapy, patients undergo CRS. Beginning 4-8 weeks after CRS, patients receive paclitaxel IV over 60 minutes on days 1, 8, and 15 and carboplatin IP over 30-60 minutes on day 1. Treatment repeats every 21 days for up to 3 courses in the absence of disease progression or unacceptable toxicity Experimental: Arm II (paclitaxel, carboplatin, CRS, HIPEC) Control arm: Patients receive paclitaxel IV over 90 minutes on days 1, 8, and 15 and carboplatin IV over 30-60 minutes on day 1. Treatment repeats every 21 days for up to 6 courses in the absence of disease progression or unacceptable toxicity. Beginning 4-8 weeks after 6 courses of chemotherapy, patients undergo CRS. Patients then receive carboplatin IP over 120 minutes immediately following CRS	USA	P	Recruiting
NCT01628380	Phase 3 Trial Evaluating Hyperthermic Intraperitoneal Chemotherapy in Upfront Treatment of Stage IIIC Epithelial Ovarian Cancer (CHORINE)	EOC	Experimental arm: neoadjuvant chemotherapy followed by CRS + HIPEC with CDDP + Paclitaxel Control arm: neoadjuvant chemotherapy followed by CRS alone	Italy	P	Unknown
NCT02328716	Cytoreduction with or without Intraoperative Intraperitoneal Hyperthermic Chemotherapy (HIPEC) in Patients with Peritoneal Carcinomatosis From Ovarian Cancer, Fallopian Tube or Primary Peritoneal Carcinoma	EOC, FTC, PPC	Procedure: Cytoreduction Drug: HIPEC with cisplatin	Spain	P	Unknown

Table 4 (*continued*)

Table 4 (*continued*)

Clinical trial number	Title of trial	Type of tumor	Trial design	Country	Primary/ Recurrence	State of trial
NCT01091636	Intraoperative Hyperthermic Intraperitoneal Chemotherapy with Ovarian Cancer	EOC	Experimental arm: HIPEC in Patients with ovarian cancer followed by adjuvant chemotherapy	Korea	P	Unknown
NCT03772028	Primary Cytoreductive Surgery with or without Hyperthermic Intraperitoneal Chemotherapy (HIPEC) (OVHIPEC-2)	EOC	Experimental arm: Primary CRS+HIPEC with cisplatin Control arm: Primary CRS	Netherlands	P	Not yet recruiting
NCT03180177	Efficacy of HIPEC as NACT and Postoperative Chemotherapy in the Treatment of Advanced-Stage Epithelial Ovarian Cancer	EOC, FTC, PPC	Experimental arm: HIPEC with paclitaxel 175 mg/m^{2}and cisplatin 75 mg/m^2 intraperitoneally in succession, 2 cycles of neoadjuvant chemotherapy: paclitaxel 175 mg/m^2 IV>3 hour+ carboplatin AUC =5-6 IV>1 hour, every 3 weeks; Interval debulking surgery + HIPEC with paclitaxel 175 mg/m^2 and cisplatin 75 mg/m^2 intraperitoneally in succession, followed by 2 cycles of adjuvant chemotherapy: paclitaxel 175 mg/m^2 IV>3 hour+ carboplatin AUC =5-6 IV>1 hour, every 3 weeks Control arm: 3 cycles of neoadjuvant chemotherapy: paclitaxel 175 mg/m^2 IV>3 hour+ carboplatin AUC =5-6 IV>1 hour, every 3 weeks; Interval debulking surgery followed by 2 cycles of adjuvant chemotherapy: paclitaxel 175 mg/m^2 IV>3 hour+ carboplatin AUC =5-6 IV>1 hour, every 3 weeks	China	P	Not yet recruiting
NCT01376752	Hyperthermic Intra-Peritoneal Chemotherapy (HIPEC) in Relapse Ovarian Cancer Treatment (CHIPOR)	EOC	Experimental arm: CRS+HIPEC with 75 mg/m^2 of cisplatin Control arm: CRS	France	R	Recruiting
NCT00426257	Secondary Debulking Surgery +/- Hyperthermic Intraperitoneal Chemotherapy in Stage III Ovarian Cancer (OVHIPEC)	EOC	Experimental arm: Secondary CRS+HIPEC Control arm: Secondary CRS	Netherlands	R	Completed

Table 4 (*continued*)

Table 4 (*continued*)

Clinical trial number	Title of trial	Type of tumor	Trial design	Country	Primary/ Recurrence	State of trial
NCT01539785	Hyperthermic Intra-peritoneal Chemotherapy (HIPEC) in Ovarian Cancer Recurrence (HORSE)	EOC	Experimental arm: CRS followed by HIPEC in patients with platinum-sensitive first recurrence of ovarian cancer Contol arm: vCRS alone	Italy	R	Unknown
NCT03220932	Cytoreductive Surgery and HIPEC in First or Secondary Platinum-resistant Recurrent Ovarian Epithelial Cancer (HIPOVA-01)	EOC	All patients will start with three cycles of CT-BEV 15 mg/kg, and will then be randomly Experimental arm: Then one cycle of monochemotherapy without bevacizumab is administered and followed by an interval CRS+HIPEC with adjuvant chemotherapy and bevacizumab (CT-BEV - 15 mg/kg once every 3 weeks) until disease progression Control arm: Chemotherapy and bevacizumab (CT-BEV) once every 3 weeks from enrollment until disease progression	France	R	Not yet recruiting
NCT03371693	Cytoreductive Surgery (CRS) Plus Hyperthermic Intraperitoneal Chemotherapy (HIPEC) with Lobaplatin in Advanced and Recurrent Epithelial Ovarian Cancer (HIPECOV)	EOC	Experimental arm: CRS+HIPEC and platinum-based intravenous chemotherapy A single drug lobaplatin (30 mg/m^2) will be administered in normal saline via HIPEC and it will be continued for 60 minutes in the hyperthermic phase (41°C-43°C). HIPEC will be performed at the 1st, 3rd and 5th day after CRS. The intravenous chemotherapy (IVCT) will start from 7th-14th day after CRS Control arm: Only CRS and IVCT. Patients will receive standard platinum-based combination doublet chemotherapy for 6-8 cycles after CRS	China	R	Active, not recruiting
NCT01767675	Outcomes After Secondary Cytoreductive Surgery with or without Carboplatin Hyperthermic Intraperitoneal Chemotherapy (HIPEC) Followed by Systemic Combination Chemotherapy for Recurrent Platinum-Sensitive Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	EOC, FTC, PPC	Experimental arm: Secondary CRS+HIPEC with carboplatin followed by systemic combination chemotherapy 5 cycles for recurrent platinum-sensitive ovarian, fallopian tube, or primary peritoneal cancer. Patients will be randomized intraoperatively to undergo CRS with HIPEC (arm A) or CRS only (arm B) in a manner 1:1. Both arms will receive a standard platinum-based systemic chemotherapy postoperatively (5 cycles in arm A and 6 cycles in arm B). In some patients randomized to HIPEC at MSKCC only, peritoneal fluid and blood samples will be drawn before, during and after the HIPEC procedure Control arm: Secondary CRS alone followed by systemic combination chemotherapy 6 cycles	USA (MSKCC)	R	Active, not recruiting

Eoc, epithelial ovarian cancer; P, primary; R, recurrence; CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; FTC, Fallopian tube cancer; PPC, primary peritoneal carcinoma; IVCT, intravenous chemotherapy; underline cells, recruiting.

Table 5 Retrospective observational studies focus on intraperitoneal chemotherapy for recurrent EOC

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO (Inclusion of persistent EOC[$]?)	IP therapy technique	No. of pts	Treatment and Chemotherapy regimen^	Platinum-Sensitive pts	CC0-1 n (%)	Median OS (months) [5y-OS%]		Median DFS or PFS° (months) [5y-DFS%]		Morbidity (3-4 grade/severe) %	Mortality %
HIPEC															
Amira (33)	2018	Ca-Co	rEOC	– (no)	HIPEC	15 ca	CRS + HIPEC with Cis 100 mg/m^2	100% Platinum-S	–	36		6		–	13.3
						20 co	Carboplatin + Taxol EV			38		5			
Arjona-Sanchez (34)	2018	Cohort	rEOC	IIIc-IV with down-staging after NACT (no)	HIPEC	100	NACT with IV Carboplatin + Taxol (or Doxo for platinum-resistant) + HIPEC with Paclitaxel 60 mg/m^2	98% Platinum-S, 2% Platinum-R	CC-0: 92 (92) CC-1: 8 (8)	48.2 [64]	CC-0: 49.3 [59], CC-1: 31.6 [35]. Negative lymph nodes: 49.3 [58]; Positive lymph nodes: 42.6 [46]	–		16	0
Baiocchi (35)	2016	Ca-Co	rEOC	I-IV (no)	HIPEC	50 ca	CRS + HIPEC with MMC 10 mg/m^2 + Cis (50 mg/m^2): 15 pts; Cis (50 mg/m^2) + Doxo: 8 pts; Oxa: 3 pts; Cis: 3 pts	100% Platinum-S	CC-0: 60 (77.9) CC-1: 9 (11.7) CC-2,3: 8 (10.4)	58.3 [49.7]		15.8		69.0 (34.5)	0
						29 co	CRS			59.3 [49.5]		18.6		42.6 (10.6)	4
Bakrin (36)	2012	Cohort	rEOC	– (yes)	HIPEC	246	Platinum-based CT before surgery + CRS + HIPEC with Cis alone or with Doxo/Mito	Platinum-S 184 (74.8), Platinum-R 62 (25.2)	CC-0,1: 247 (92.2), CC-2,3: 21 (7.8)	48.9 [35]	Platinum-R:48, Platinum-S: 52	12.8 [9]		(11.6)	0.37
Carrabin (37)	2010	Cohort	rEOC	IIIC (yes)	HIPEC	18 (8 recur-rent, 10 persistent)	CRS+HIPEC with Oxa 460 mg/m^2	Platinum-S 7 (87.5), Platinum-R: 1 (12.5)	CC-0: 16 (88.9), CC-1: 2 (11.1)	Not reached, 2y-OS 92%, 3y-OS 83%		11.3		(55.6)	0
Cascales-Campos (38)	2015	Ca-Co	rEOC	I-IV (no)	HIPEC	Ca 32	Pre-op Platinum + Taxanes EV if unresectable + CRS+HIPEC with Paclitaxel 60 mg/m^2	100% Platinum-S	CC-0 54 (100)	–		3y DFS: 45		28 (21)	0
						Co 22	Pre-op Platinum + Taxanes EV if unresectable + CRS					3y DFS: 23		23 (14)	
Chatzigeorgiou (39)	2003	Cohort	rEOC	–	HIPEC	20	CRS+HIPEC with Cis 50-70 mg/m^2	30% Platinum-S, 70% Platinum-R	Residual tumor (RT). <1.5 cm: 12 (60), >1.5 cm: 8 (40)	RT <1.5 cm: 29, RT >1.5 cm: 7. Platinum-S: 27, Platinum-R: 9		–		15	5
Cianci (40)	2019	Cohort	rEOC (previous CRS+HIPEC)	– (no)	Tertiary HIPEC	12	Tertiary CRS + HIPEC with Oxa 360 mg/m^2 or Cis 75 mg/m^2	100% Platinum-S	100% RT=0	Mean OS 99		28		24.9 (8.3)	0
Classe (41)	2015	Cohort	rEOC (first relapse)	(yes)	HIPEC	314	(Ev. second-line IV CT) + CRS + HIPEC with Cis	Platinum-R 52.9% Platinum-S 47.1%	CC-0: 248 (79) CC-1.2: 66 (21)	[38]	Platinum-S: 42 Platinum-R: 51 CC-0: 54 CC-1.2: 36	[14]	Platinum-S: 13 Platinum-R: 14 CC-0: 15 CC-1,2: 10	(30.9)	1
Cotte (42)	2007	Cohort	rEOC	(yes)	HIPEC	Persistence of disease + Platinum-R recurrence 16	CRS + HIPEC with Cis 20 mg/m^2/L	Platinum-R 19.8% Platinum-S 80.2%	CC-0: 45 (55.5) CC-1: 20 (24.7) CC-2: 16 (19.8)	24.3	PCI<12: 37.6, PCI>12: 13.1; CC-0: 54.9, CC-1: 17.0, CC-2: 5.1	8.0	PCI<12: 12.8, PCI>12: 2.4; CC-0: 47.8	(13.6)	2.5
						Platinum-S recurrence 65				28.4		8.5			
Delotte (43)	2014	Cohort	rEOC >70 y	– (no)	HIPEC	15	CRS+HIPEC with Cis 50 mg/m^2 + Doxo 15 mg/m^2	–	CC-0: 9 (60), CC-1: 6 (40)	35		15.6		(20)	0
Deraco (44)	2001	Cohort	rEOC	I-IV (yes)	HIPEC	27	CRS+HIPEC with Cis 25 mg/m^2/L + MMC 3.3 mg/m^2/L	–	CC-0: 15 (55), CC-1: 4 (15), CC-2: 3 (11), CC-3: 5 (19)	[2yOS: 55%]	CC-0,1: 20.3 [2yOS 77%], CC-2,3: 4.3 [2yOS 0%]	21.8 [2yDFS: 21%]		11	4

Table 5 (*continued*)

Table 5 (*continued*)

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO (Inclusion of persistent EOC[$]?)	IP therapy technique	No. of pts	Treatment and Chemotherapy regimen^	Platinum-Sensitive pts	CC0-1 n (%)	Median OS (months) [5y-OS%]	Median DFS or PFS° (months) [5y-DFS%]	Morbidity (3-4 grade/severe) %	Mortality %
Deraco (45)	2012	Cohort	rEOC	I-IV (no)	HIPEC	56	CRS+HIPEC with Cis 42 mg/L + Doxo 15 mg/L or Cis 25 mg/L/m^2 + MMC 3.3 mg/L/m^2	Platinum-S 58.9% Platinum-R 23.1%	CC-0: 46 (83.9) CC-1: 7 (12.5) CC-2: 1 (1.8)	25.7 [23]	10.8 [7]	(26.3)	5.3
Fagotti (46)	2009	Cohort	rEOC	I-IV (yes)	HIPEC	25	CRS+HIPEC with Oxa 460 mg/m^2 + post-op IV Oxa + Docetaxel	Platinum-S 100%	CC-0: 23 (92) CC-1: 2 (8)	–	10	(28)	0
Fagotti (47)	2012	Ca-Co	rEOC	I-IV (yes)	HIPEC	30 Ca	CRS+HIPEC with Oxa 469 mg/m^2 + post-op IV platinum CT	Platinum-S 100%	CC-0: 29 (96.7) CC-1: 1 (3.3)	[68.4]	26	(34.8)	0
						37 Co	CRS+IV CT (35%) or IV CT (65%)		–	[42.7]	15		
Fagotti (48)	2014	Cohort	rEOC (single nodule)	Single nodule (no)	Laparoscopic HIPEC	10	Laparoscopic/robotic CRS+HIPEC with Oxa 469 mg/m^2 or Cis 75 mg/m^2 + post-op IV carboplatin-paclitaxel CT	Platinum-S 100%	CC-0: 100%	–	–	10	0
Fahim (49)	2018	Cohort	rEOC	(no)	HIPEC	9	CRS+HIPEC with Cis 200 mg/m^2	Platinum-S 100%	–	42	Not reached	–	22.2
Furet (50)	2013	Cohort	rEOC	–	HIPEC	17	CRS+HIPEC with Oxa 460 mg/m^2 + IV 5FU 400 mg/m^2 or Carbo 400-1200 mg/m^2	–	CC-0: 16 (94)	mean OS: 30.5	11.9	47 (17.6)	0
Gomez-Ruiz (51)	2019	Cohort	rEOC	I-IV (–)	HIPEC	64	CRS+HIPEC with Paclitaxel 60 mg/m^2 or Cis 75 mg/m^2	Platinum-S 100%	CC-0: 57 (89) CC-1: 7 (11)	–	17 [30]	–	–
Helm (52)	2007	Cohort	rEOC	IIIC-IV	HIPEC	18	CRS+HIPEC with Cis 100 mg/m^2 or MMC 40 mg	–	CC-0: 11 (61.1) CC-1: 6 (33.4) CC-2: 1 (5.5)	31, RT<2 mm: 31, RT>2 mm: 8	10	100 (72)	5.5
Konigsrainer (53)	2011	Cohort	rEOC	IIIb-IV (–)	HIPEC	31	CRS+HIPEC with Cis 50mg/m^2	–	CC-0: 20 (65) CC-1: 8 (25) CC-2: 3 (10)	[3y-OS 50%]	[3y-DFS 15%]	23	0
Konigsrainer (54)	2014	Cohort	rEOC	I-IV (–)	HIPEC	CC-0,1: 62	CRS+HIPEC with Cis 50 mg/m^2	Platinum-R 13% Platinum-S 87%	CC-0: 47 (52) CC-1: 15 (17)	35	–	45 (26)	0
						CC-2,3: 28			CC-2: 5 (6) CC-3: 23 (26)	14		36 (11)	0
Le Brun (55)	2014	Ca-Co	rEOC	I-IV (yes)	HIPEC	Ca 23	CRS+HIPEC with Cis, Eloxatin, MMC	Platinum-S 100%	CC-0: 42 (100)	[4y-OS 75.6]	–	–	–
						Co 19	CRS			[4y-OS 19.4]			
Marocco (56)	2016	Ca-Co	rEOC	I-IV (yes)	HIPEC	16	IV platinum-based CT	Platinum-S 100%	–	35.6	13.2	0 (0)	0
						11	CRS + IV platinum-based CT		CC-0 100%	Not reached	23	36 (0)	0
						19	IV platinum-based CT + CRS + HIPEC with Cis 100 mg/m^2 + Doxo 15.2 mg/L			51.5	19.9	32 (16)	0
Munoz-Casares (57)	2009	Ca-Co	rEOC	III	HIPEC	14 Ca	CRS+HIPEC with Paclitaxel 60 mg/m^2 + post-op IV CT	–	CC-0: 16 (61.5) CC-1: 10 (38.5)	[57] [for CC-0 67]	Mean DFS 48	29 (14)	0
						12 Co	CRS + post-op IV CT			[17] [for CC-0 29$_1$	Mean DFS 24	25 (25)	0
Petrillo (58)	2016	Cohort	rEOC	I-IV	HIPEC	70	CRS + HIPEC with Oxa 460 mg/m^2 or Cis 75 mg/m^2	Platinum-S 100%	CC-0: 62 (88.6) CC-1: 8 (11.4)	–	27	35.7 (8.5)	0

Table 5 (*continued*)

Table 5 (*continued*)

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO (Inclusion of persistent EOC[§]?)	IP therapy technique	No. of pts	Treatment and Chemotherapy regimen^	Platinum-Sensitive pts	CC0-1 n (%)	Median OS (months) [5y-OS%]	Median DFS or PFS° (months) [5y-DFS%]	Morbidity (3-4 grade/severe) %	Mortality %
Safra (59)	2014	Ca-Co	rEOC	I-II-III (no)	HIPEC	26	CRS + HIPEC Cis 50 mg/m^2 + Doxo 15 mg/m^2 or Paclitaxel 60 mg/m^2 + Carbo or Cis 25 mg/L/m^2 + MMC 3.3 mg/L/m^2	Platinum-S 100%	CC-0: 110 (100)	Not reached [79]; BRCA wt: 61.6; BRCA mut: 80.1	15, BRCA wt: 21.8, BRCA mut: 20.9	–	–
						84	IV CT with Carbo + Paclitaxel or Doxo or Gemcitabine or Topotecan			[45] BRCA wt: 47.7, BRCA mut: 71.6	6, BRCA wt: 12.1, BRCA mut: 12.6		
Spiliotis (60)	2019	Ca-Co	rEOC	– (yes)	HIPEC	80 with residual disease + 30 with recur-rent disease	CRS + HIPEC with + post-op IV CT	Platinum-S 100%	Residual disease: CC-0 (75) Recurrent disease: CC-0 (64)	Residual disease: 38 Recurrent disease: 26	–	Residual disease: 18; Recurrent disease: 22	Residual disease: 2.5; Recurrent disease: 3.3
						60 with residual disease + 20 with recur-rent disease	CRS + post-op IV CT			Residual disease: 23.8, Recurrent disease: 16		Residual disease: 7; Recurrent disease: 15	Residual disease: 1.3; Recurrent disease: 0
Van der Vange (61)	2000	Cohort	rEOC	–	HIPEC	5	CRS + HIPEC with Cis 50–70 mg/m^2	–	CC-0,1: 5 (100)	–	–	60	0
Vernaccini (62)	2016	Ca-Co	rEOC with PCI>20	IIIB-IV (yes)	HIPEC	9 Ca	CRS + HIPEC	–	CC-1 (57.1), CC-2 (42.9)	3 months-OS 77.8%, 1 y-OS 55.6%	–	–	–
						5 Co	CRS			3 months-OS 60%, 6 months-OS 0%			
Zivanovic (63)	2014	Ca-Co	rEOC	IIIB-IIIC-IV	HIPEC	3	CRS + HIPEC with Cis 60 mg/m^2	Platinum-S 100%	CC-0: 7 (58), CC-1: 1 (8), CC-2: 4 (34)	–	13.6	DLT 0	0
						3	CRS + HIPEC with Cis 80 mg/m^2					DLT 0	0
						6	CRS + HIPEC with Cis 100 mg/m^2					DLT 16.7	0
Other intraperitoneal chemotherapy													
Lu C (64)	2015	Propensity score	rEOC	I-IV (yes)	IP	155 Ca	CRS + IP platinum-based CT	Platinum-S 216 (69.7); Platinum-R 94 (30.3)	RT=0: 77 (24.8); RT<1 cm: 86 (27.7); RT>1 cm: 147 (47.4)	–	Platinum-S: 9.8, Platinum-R: 4.9	–	–
						155 Co	CRS+IV CT				Platinum-S: 6.9, Platinum-R: 2.4		
Plaisant (65)	2004	Cohort	rEOC	IC-IV (yes)	IP	9 persistent EOC	CRS + IP CT with Paclitaxel 175 mg/m^2	–	CC-0: 8 (61.5); CC-1: 2 (15.5); CC-2: 3 (23)	25.5	8.5	11.7 (92)	7.7
						4 rEOC					4.2		

[§]EOC with sub-optimal cytoreduction at primary surgery and evidence of persistent peritoneal disease; Cis, Cisplatin; Doxo, Doxorubicin; MMC, Mitomycin C; Oxa, Oxaliplatin; Carbo, Carboplatin; Ca-Co, case-control; CT, Chemotherapy; rEOC, recurrent EOC; pEOC, primary EOC; cEOC, HIPEC for consolidation. NA, not available; DLT, dose limiting toxicity.

Table 6 Prospective studies focus on intraperitoneal chemotherapy for recurrent EOC

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO (Inclusion of persistent EOC[§]?)	IP therapy technique	no. of pts	Chemotherapy regimen	Platinum Sensitive pts	CC0-1 n (%)	OS (months) [5y-OS%]	DFS or PFS° (months)	Morbidity (3-4 grade/ severe) %	Mortality %
HIPEC													
Argenta (66)	2013	Cohort	rEOC	– (no)	HIPEC	10	CRS+HIPEC with Carboplatin 1,000 mg/m^2 + IV ACT: Carboplatin + Taxol 6 cycles	Platinum-S 100%	CC-0: 6 (60); CC-1,2: 4 (40)	1 death after 15 months	3 recurrences with a mean FU of 16 months	–	0
Fagotti (67)	2011	Cohort	rEOC	I-IV (yes)	HIPEC	41	CRS+HIPEC with Oxa 460 mg/m^2 + post-op IV Docetaxel + Oxa	Platinum-S 100%	CC-0: 41 (95.3); CC-1: 2 (4.7)	38 [3yOS 92%]	24 [3yDFS 44%]	(34.8)	0
Petrillo (68)	2019	Case -control	rEOC	–	HIPEC	11	Open CRS+HIPEC with Cis 75 mg/m^2	Platinum-S 100%	CC-0,1: 20 (100)	–	3y-DFS: 60.5 3y-DFS: 58.3	20 (10) 27.3 (9.1)	0
						9	Minimally-invasive CRS+HIPEC with Cis 75 mg/m^2				3y-DFS:70.6	11.1 (11.1)	0
Spiliotis (18)	2015	RCT	rEOC	IIIC-IV	HIPEC	60	CRS+HIPEC with Cis 100 mg/m^2 + Paclitaxel 175 mg/m^2 for platinum-S or Doxo 35 mg/m^2+ Paclitaxel 175 mg/m^2 or MMC 15 mg/m^2 for platinum-R	Platinum-S: 38 (63.3); Platinum-R: 22 (36.7)	CC-0: 39 (65); CC-1: 12 (20); CC-2: 9 (15)	Mean OS 26.7; Stage IIIC: 26.9, Stage IV: 26.4; Platinum-S: 26.8, Platinum-R: 26.6; CC-0: 30.9, CC-1: 23.9, CC-2: 12.1	–	–	–
						60	CRS + post-op IV CT	Platinum-S: 36 (60); Platinum-R: 24 (40)	CC-0: 33 (55); CC-1: 20 (33.3); CC-2: 7 (11.7)	Mean OS: 134; Stage IIIC: 14.2, Stage IV: 11.9; Platinum-S: 15.2, Platinum-R: 10.2; CC-0: 16.1, CC-1: 11, CC-2: 6.7	–	–	–
Zanon (69)	2004	Cohort	rEOC		HIPEC	30	CRS+HIPEC with Cis 100-150 mg/m^2	–	CC-0,1: 23 (77); CC-2: 7 (23)	28.1 [2y-OS 60%], CC-0,1: 3.8, CC-2: 11.0	Regional DFS: 17.1; CC-0,1: 24.4, CC-2: 4.1	43.7 (16.7)	3.3
Other intraperitoneal chemotherapy													
Jandial (70)	2017	Cohort	rEOC	(yes)	EPIC	32	IP Bortezomib + Carbo on day 1 of a 21-day cycle for 6 cycles	–	–	–	4.9	–	0
Tempfer (71)	2014	Cohort	rEOC	–	PIPAC	10	PIPAC with Cis 7.5 mg/m^2 + Doxo 1.5 mg/m^2 repeated after 4–6 weeks until progression or limiting toxicity	–	–	14.7 [2y-OS: 65%] 8.9 [2y-OS: 58%]	–	(27.7)	0
						8	CRS+PIPAC Cis 7.5 mg/m^2 + Doxo 1.5 mg/m^2 repeated after 4–6 weeks until progression or limiting toxicity			16.1 [2y-OS: 75%]	–		
Tempfer (72)	2015	Cohort	rEOC	–	PIPAC	34	PIPAC with Cis 7.5 mg/m^2 + Doxo 1.5 mg/m^2 repeated three times every 4–6 weeks	Platinum-R 100%	–	13.6 [1y-OS:63]	5.8	–	0
Tempfer (73)	2018	Cohort	rEOC	–	PIPAC	3	PIPAC with Cis 7.5 mg/m^2 + Doxo 1.5 mg/m^2 q 4 to 6 weeks for 3 courses	–	–	–	Histologic tumor regression 64%	No DLT found (6.7)	6.7
						7	PIPAC with Cis 9 mg/m^2 + Doxo 1.8 mg/m^2 q 4 to 6 weeks for 3 courses						
						5	PIPAC with Cis 10.5 mg/m^2 + Doxo 2.1 mg/m^2 q 4 to 6 weeks for 3 courses						

[§]EOC with sub-optimal cytoreduction at primary surgery and evidence of persistent peritoneal disease; Cis, Cisplatin; Doxo, Doxorubicin; MMC, Mitomycin C; Oxa, Oxaliplatin; Carbo, Carboplatin; Ca-Co, case-control; rEOC, recurrent EOC; pEOC, primary EOC; cEOC, HIPEC for consolidation; NA, not available; DLT, dose limiting toxicity.

Table 7 Retrospective observational studies focus on intraperitoneal chemotherapy for primary and recurrent EOC

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO (Inclusion of persistent EOC[§]?)	IP therapy technique	no. of pts	Treatment and Chemotherapy regimen	Platinum-Sensitive pts	CC0-1 n (%)	Median OS (months) [5y-OS%]	Median DFS or PFS° (months) [5y-DFS%]	Morbidity (3-4 grade/severe) %	Mortality %
Arjona-Sanchez (74)	2017	Cohort	pEOC	IIIC-IV	HIPEC	320	CRS+HIPEC with Paclitaxel 60 mg/m^2 or Cis 75 mg/m^2	–	CC-0: 500 (95) CC-1,2: 27 (5)	1997-2004: 38 [37]; 2005-2009: [48]; 2010-2012: 57 [49]; 2012-2016: 43	1997-2004: 25; 2005-2009: –; 2010-2012: 24; 2012-2016: 27	(15)	2
			rEOC			207				1997-2004: 57 [51]; 2005-2009: [48]; 2010-2012: 55 [47]; 2012-2016: 35	1997-2004: 31; 2005-2009: –; 2010-2012: 19; 2012-2016: 27		
Bakrin (75)	2013	Cohort	pEOC	–	HIPEC	36	(ev. NACT) + CRS + HIPEC with Cis, MMC, Doxo, Oxa	–	CC-0: 423 (74.3)	35.4	11.8	(31.3)	0.8
			cEOC			56							
			rEOC			477		Platinum-S: 46.8%, Platinum-R: 51.8%		45.7	–		
Barakat (76)	2002	Cohort	rEOC	II-IV (yes)	IP	322	Platinum-based combination IP CT at the time of second-look assessment	–	–	Microscopic disease: 57.6; Disease >1 cm: 14.4; Disease <1 cm: 39.6	Microscopic disease: 26.3, Gross disease: 16.3	22.6	–
			cEOC			89				104.4	32		
Cascales-Campos (770)	2014	Cohort	pEOC	IIIB-IV	HIPEC	22	CRS+HIPEC with Paclitaxel 60 mg/m^2 or Cis 75 mg/m^2	Platinum-S 100%	CC-0: 73(80.2) CC-1: 18 (19.8)	–	–	27 (12)	0
						38	NACT+CRS+HIPEC with Paclitaxel 60 mg/m^2 or Cis 75 mg/m^2						
			rEOC			31	CRS+HIPEC with Paclitaxel 60 mg/m^2 or Cis 75 mg/m^2						
Cripe (78)	2015	Cohort	pEOC, rEOC, cEOC	I-IV (no)	HIPEC	24 rEOC, 6 pEOC, 2 cEOC	CRS + HIPEC with Oxa 460 mg/m^2 + IV 5-FU or MMC 20 mg/m^2 or Oxa 460 mg/m^2 or Cis 75 mg/m^2 or Cis 40 mg/m^2 + Doxo 12 mg/m^2 or Doxo 15 mg/m^2	Platinum-S 100%	CC-0: 29 (90.6), CC-1: 2 (6.3), CC-2: 1 (3.1)	–		–	(65.6)	0
Di Giorgio (79)	2017	Cohort	pEOC	III-IV	HIPEC	226	CRS+HIPEC with Oxa 460 mg/m^2 or Cis 75 mg/m^2 or Cis 75 mg/m^2 + Doxo/Paclitaxel/ MMC	–	CC-0: 160 (70.8)	52.4 [4.4]	16.6 [19.7]	44.2 (17.4)	2.5
										54.2 PDS: 61.2 prNACT + IDS: 58 nrNACT + IDS: 34.7 crNACT + IDS: NR	20,2 PDS:29,9 prNACT + IDS: 15 nrNACT + IDS: 14.5 crNACT + IDS: NR		
			rEOC			285			CC-0: 211 (74)				
										46.8. fr PFS >12 months: 96.3; fr PFR <12 months: 35.7; fr PFS >12 months further CT: 48.3; more CRS and more chemo-therapy before HIPEC: 35.7	15.2. fr PFS >12 months: 17.5; fr PFR <12 months: 12.4; fr PFS>12 months further CT: 14.2; more CRS and more chemo-therapy before HIPEC: 15.4		
Frenel (80)	2011	Cohort	pEOC	IIIC-IV	HIPEC	19	(ev NACT) + CRS+HIPEC with Oxa 360-460 mg/m^2	–	CC-0: 31 (100)	–	13.2 [1y-DFS 59.3%]	(29)	0
			rEOC			12					14.3 [1y-DFS 54.4%]		
Helm (20)	2010	Cohort	pEOC	II-IV	HIPEC	45	(ev NACT) + CRS+HIPEC with Carbo or Cis or Cis + Doxo or Oxa or MMC or Carbo + MMC	Platinum-S: 61.3%, Platinum-R: 38.7	CC-0: 81 (58.3); CC-1: 21 (15.1); CC-2: 30 (21.6) CC-3: 7 (5.0)	Upfront: 41.7 [33.3] Interval: 68.9 [50.2]	Upfront: 24.8 [19.7] Interval: 16.8 [9.6]	–	–
			cEOC			12				53.7 [42.4]	29.6 [24.2]		
			rEOC			83				23.5 [18]	13.7 [9.6]		

Table 7 (*continued*)

Table 7 (*continued*)

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO (Inclusion of persistent EOC[§]?)	IP therapy technique	no. of pts	Treatment and Chemotherapy regimen	Platinum-Sensitive pts	CC0-1 n (%)	Median OS (months) [5y-OS%]		Median DFS or PFS° (months) [5y-DFS%]	Morbidity (3-4 grade/severe) %	Mortality %
Manzanedo (81)	2017	Cohort	pEOC	IIIC-IV (no)	HIPEC	31 (4 up-front, 27 inter-val)	NACT if not resectable pEOC, CT before surgery in all rEOC + CRS+HIPEC with Taxol 60 mg/m^2 or Cis 100 mg/m^2 + Doxo 15 mg/m^2	–	CC-0: 56 (92); CC-1: 3 (5); CC-2: 2 (3)	Not reached [55]	Up-front CRS: [100]; Interval CRS: 40 [46.5]	12	52.5 (29.5)	0
			rEOC			30		20 Platinum-S, 10 Platinum-R		50 [47,1]	Platinum-S: 59 [38.3]; Platinum-R: Not reached [56]	17		
Massari (82)	2014	Cohort	pEOC	III-IV (no)	HIPEC	14 (2 up-front, 12 inter-val)	CRS + HIPEC with Cis 60 mg/m^2/L + Doxo 20 mg/ m^2/L or Taxotere 60 mg/m^2/L + Doxo 20 mg/m^2/L	–	CC-0: 14 (56); CC-1: 8 (32); CC-2,3: 3 (12)	36.5	CC-0,1: 32.8; CC2,3: 14; PCI 15: 42; PCI >15: 11	12.9	56 (16)	8
			rEOC			11				27		11.9		
Pavlov (83)	2009	Cohort	pEOC	IIIC-IV	HIPEC+EPIC	31	CRS+HIPEC with Doxo 0.1 mg/kg/day + EPIC with Cis 15 mg/m^2 for 5 days	–	CC-0,1: 52 (92.8) CC-2,3: 4 (7.2)	34.1	PCI >12: [38]; PCI <12: [83]	26.2	15	3
			rEOC			25				40.1				
Pavlov (84)	2018	Cohort	pEOC	–	HIPEC+EPIC	55	CRS+EPIC with Doxo 0.1 mg/kg for 2 hours + Cis 15 mg/m^2 for 5 days or HIPEC with Cis 15 mg/m^2 + Doxo 0.1 mg/kg	–	CC-0,1: 70 (62.5) CC-2,3: 1 (25)	40.3 [24]		–	9.5 (1.7)	0.86
			rEOC			61		Platinum-R 13.1% Platinum-S 86.9%	CC-0,1: 42 (37.5) CC-2,3: 3 (75.0)	27.6 [3y-OS 16]				
Piso (85)	2004	Cohort	pEOC	IIIC-IV	HIPEC	8	(ev NACT) + CRS + HIPEC with Cis 75 mg/m^2 or Mitoxantrone 15 mg/m^2	–	CC-0: 9 (47.3)	29		18	(36.8)	5.7
			rEOC			11				30				
Raspagliesi (86)	2006	Cohort	rEOC+pEOC	III-IV	HIPEC	40	CRS+HIPEC with Cis 25 mg/m^2/L + MMC 3.3 mg/m^2/L or Cis 43 mg/L + Doxo 15.25mg/L	–	CC-0: 33 (82.5) CC-2: 7 (17.5)	Mean OS: 41.4 [15]		Mean DFS: 23.9	20	0
Robella (87)	2014	Cohort	pEOC	III-IV (no)	HIPEC	45	CRS + HIPEC with Cis 100 mg/m^2 + Doxo 15.2 mg/L	–	CC-0: 55 (78.6) CC-1: 9 (12.8) CC-2: 6 (8.6)	48.0	CC-0: 48 [92]; CC-1: 24 [58]; CC-2: 9 [41]; PCI ≤16: 46 [45]; PCI >16: 28 [24]	–	35.7 (12.8)	7.1
			rEO			25				28.0				
Roviello (88)	2010	Cohort	pEOC	IIIA-IIIC (yes)	HIPEC	14	Primary CRS + post-op IV CT + CRS+HIPEC with MMC 25 mg/m^2 + Cis 100 mg/m^2 + post-op IV CT		CC-0: 11 (79) CC-1: 1 (7) CC-2,3: 2 (14)	[55]	PCI 0: [100]; PCI 1-6: [48]; PCI>6 [0]; CC-0: [71]; CC-1: [44]; CC-2,3: [0]	CC-0: [54]	42 (23)	0
						31	NACT + CRS + HIPEC with MMC 25 mg/m^2 + Cis 100 mg/m^2 + post-op IV CT		CC-0: 20 (64) CC-1: 4 (13) CC-2,3: 7 (23)	[58]				
			rEOC			8	CRS+HIPEC with MMC 25 mg/m^2 +Cis 100 mg/m^2 + post-op IV CT		CC-0: 6 (75) CC-1: 2 (25)	[44]				
Rufian (89)	2006	Cohort	pEOC	III	HIPEC	19	CRS+HIPEC with Paclitaxel 60 mg/m^2 + post-op IV CT	–	CC-0: 17 (52) CC-1,2: 16 (48)	38 [37]	CC-0:[60]	25	(36)	0
			rEOC			14				57 [51]	/	31		
Sanchez-Garcia (90)	2016	Cohort	pEOC	II-III-IV	Modified HIPEC[c]	16	CRS+HIPEC with Paclitaxel 175 mg/m^2	–	–	–		–	95.24 (38.1)	4.8
			rEOC			5								

Table 7 (*continued*)

Table 7 (*continued*)

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO (Inclusion of persistent EOC[§]?)	IP therapy technique	no. of pts	Treatment and Chemotherapy regimen	Platinum-Sensitive pts	CC0-1 n (%)	Median OS (months) [5y-OS%]		Median DFS or PFS° (months) [5y-DFS%]		Morbidity (3-4 grade/severe) %	Mortality %
Sun JH (91)	2016	Cohort	pEOC	IIIC-IV (/)	HIPEC+IP	16	CRS+HIPEC with Cis 100 mg/m^2 + MMC 20 mg/m^2 or Paclitaxel 100 mg/m^2 + Lobaplatin 50 mg/m^2 + post-op IV CT + peri-op IP with Cis 100 mg/m^2 + Paclitaxel 100 mg/m^2 or Paclitaxel 100 mg/m^2 + Doxo 35 mg/m^2 once every 3-4 weeks	–	CC-0,1: 28 (60.9) CC-2,3: 18 (39.1)	74.0	PCI <20: 76.6, PCI >20: 38.5; CC-0,1: 79.5; CC-2,3: 24.3	Not reached		10 (10)	0
			rEOC			30		Platinum-S 53.3% Platinum-R 46.7%		57.5. Platinum-S: 65.3; Platinum-R: 20.0		8.5			
Warschkow (92)	2012	Cohort	pEOC	III-IV	HIPEC	21	NACT+CRS + HIPEC with Cis 50 mg/m^2	–	CC-0: 19 (90.5)	Not reached [63]		–		28.5	0
			rEOC												
Yoshida (93)	2005	Cohort	pEOC	III	HIPEC	2	CRS+HIPEC with Cis 100 mg/m^2 + MMC 20 mg/m^2 + Etoposide 100 mg/m^2	–	–	70.2 [18]	14.5 [0]	41.2 [40]	5 [0]	–	0
						4	NACT+CRS+HIPEC with Cis 100 mg/m^2 + MMC 20 mg/m^2 + Etoposide 100 mg/m^2				38 [0]		17.75 [0]		
			cEOC			4	Second-look + HIPEC with Cis 100 mg/m^2 + MMC 20 mg/m^2 + Etoposide 100 mg/m^2				130.25 [100]		82.75 [50]		

[§]EOC with sub-optimal cytoreduction at primary surgery and evidence of persistent peritoneal disease; Cis, Cisplatin; Doxo, Doxorubicin; MMC, Mitomycin C; Oxa, Oxaliplatin; Carbo, Carboplatin; Ca-Co, case-control; rEOC, recurrent EOC; pEOC, primary EOC; cEOC, HIPEC for consolidation. NA, not available; [C] HIPEC by fluid and CO2 recirculation using the closed abdomen technique (PRS-1.0 Combat); CT, Chemotherapy; NACT, neo-adjuvant chemotherapy; prNACT + IDS, partial response NACT + interval debulking surgery; nrNACT + IDS, non-response NACT + interval debulking surgery; crNACT + IDS, complete response NACT + interval debulking surgery; fr, first recurrence.

Table 8 Prospective observational studies focus on intraperitoneal chemotherapy for primary and recurrent EOC

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO (Inclusion of persistent EOC[§]?)	IP therapy technique	no. of pts	Chemotherapy regimen	Platinum-Sensitive pts	CC0-1 n (%)	OS (months) [5y-OS%]	DFS or PFS° (months)	Morbidity (3-4 grade/severe) %	Mortality %
Ansaloni (94)	2012	Cohort	pEOC	IIIC	HIPEC	9	CRS+HIPEC with Cis 100 mg/m^2 and/or Paclitaxel 175 mg/m^2 and/or Doxo 35 mg/m^2	Platinum-S: 33%, Platinum-R: 62%	CC-0: 35 (90), CC-1: 3 (7), CC-3: 1 (3)	–	Mean DFS: 14.4	(18)	2.5
			rEOC			30							
Ansaloni (95)	2015	Cohort	pEOC	IIIC-IV	HIPEC	9	CRS+HIPEC with Cis 100 mg/m^2 and Paclitaxel 175 mg/m^2	Platinum-S: 100%	CC-0: 13 (100)	–	–	100 (61.5)	0
			rEOC			4							
Coccolini (96)	2015	Cohort	pEOC	IIIC-IV	HIPEC	30	(ev. NACT) + CRS+HIPEC with Cis 100 mg/m^2 + Paclitaxel 175 mg/m^2	Platinum-S: 68.5%, Platinum-R: 31.49%	CC-0: 47 (87), CC-1: 7 (13)	32.9 22	12.5 13	95.2 (35.2)	5.6
			rEOC			24				44	12		
Di Giorgio (79)	2008	Cohort	pEOC	IIIC-IV	HIPEC	22	CRS+HIPEC with Cis 75 mg/m^2	–	CC-0,1: 41 (87.2), CC-2,3: 6 (12.8)	27 PCI <15: 24; PCI >15: 26; CC-0: 26; CC-1: 13; CC-2,3: 12	25.5 PCI <15: 21; PCI >15: 20; CC-0: 24; CC-1: 13; CC-2,3: 6	48.9 (21.3)	4.2
			rEOC			25				22.5	15.5		
Gonzalez Bayon (97)	2013	Cohort	pEOC	IIIC-IV	HIPEC + EPIC	15	NACT + CRS + HIPEC with Cis 100 mg/m^2 + Doxo 30 mg/m^2 + ev. EPIC with Taxol 20 mg/m^2 for 5 days	–	CC-0: 11 (73.3)	77.8	21.1 (72)	26.6	6.6
			rEOC			19 first recurrence, 8 second recurrence			First recur. CC-0: 14 (73.6)	First recur. 62.8	First recur. 18.1 (62.2)	21	5.2
									Second or subsequent recurrence CC-0: 6 (75)	Second or subsequent recurrence: 35.7	Second or subsequent recurrence: 5.7 (17.9)	37.5	12.5
Pomel (98)	2010	Cohort	cEOC+rEOC	IIIC (yes)	HIPEC	31	CRS + post-op IV CT with Cis 6 cycles + second-look laparotomy + HIPEC with Oxa 460 mg/m^2	–	CC-0 31 (100)	[2y-OS 67%]	[2y-DFS 27%]	(29)	0
Tentes (99)	2012	Cohort	pEOC	–	HIPEC	23	CRS+HIPEC with Cis 50 mg/m^2 + Doxo 15 mg/m^2 or Gem 1000 mg/m^2 in Platinum-R	–	CC-0: 30 (69.8)	37	–	(14)	4.7
			rEOC			20							

[§]EOC with sub-optimal cytoreduction at primary surgery and evidence of persistent peritoneal disease; Cis, Cisplatin; Doxo, Doxorubicin; MMC, Mitomycin C; Oxa, Oxaliplatin; Carbo, Carboplatin; Gem, Gemcitabine; CT, chemotherapy; Ca-Co, case-control; rEOC, recurrent EOC; pEOC, primary EOC; cEOC, HIPEC for consolidation; NA, not available.

CRS+HIPEC or with systemic chemotherapy alone. The significant benefit in median DFS that was observed in the HIPEC group remained regardless of the patients' BRCA status (BRCAwt: 21.8 in HIPEC group *vs.* 12.1 in control group, P=0.011; BRCAmut: 20.9 in HIPEC group *vs.* 12.6 in control group, P=0.012). The observed benefit in OS remained significant in BRCAmut patients treated with HIPEC and showed a trend toward a benefit in BRCAwt patients (BRCAwt: 61.6 in HIPEC group *vs.* 47.7 in control group, P=0.068; BRCAmut: 80.1 in HIPEC group *vs.* 71.6 in control group, P=0.036).

In eight case-control studies (35,47,55-57,60,62,77), almost all focused on platinum-S patients. They compared outcomes of patients treated with CRS + HIPEC with patients treated with CRS alone for rEOC. Most of the studies (47,55,57,62) showed a significant benefit in terms of OS and DFS in patients treated with HIPEC. Other studies showed better outcomes in HIPEC group but without statistical significance (38,56,60).

There is only one RCT that included 120 patients with rEOC (FIGO IIIC-IV) comparing CRS + HIPEC + systemic chemotherapy with CRS + systemic chemotherapy. The study showed a significant higher OS in the HIPEC group (26.9 *vs.* 14.2 months in stage IIIC and 26.4 *vs.* 11.9 months in stage IV, P=0.006). Furthermore, in the HIPEC group similar OS in platinum-S and platinum-R patients was observed while in the control group the OS of platinum-S patients was significantly longer than platinum-R ones (15.2 *vs.* 10.2, P=0.002). Median OS in HIPEC group was significantly higher than in CRS group both in PCI<15 (P=0.031) and in PCI>15 patients (P=0.049). This benefit remained only in CC-0 patients (30.9 *vs.* 16.9 months, P=0.038).

The study by Spiliotis (*Table 1*) was criticized by some authors (100) regarding methods and statistical analysis. The endpoints, the randomization procedure and the systemic CT regimen were not explained and DFS, morbidity and mortality were not reported. In two recent meta-analyses (101,102) including observational studies and the only RCT on rEOC, CRS + HIPEC showed a significant advantage compared to CRS alone in terms of OS and DFS (if CC-3 patients were excluded). Almost all the studies agree in affirming the completeness of the cytoreduction (CC-0) as the major prognostic factor on OS and DFS (18,34,39,42,44,52,57,69,76). The reported major morbidity and mortality for CRS + HIPEC in patients with rEOC ranges from 8.3 to 72% and from 0 to 22.2% respectively. Then, evidence to date suggests a role for HIPEC in both platinum-R and platinum-S patients and in both BRCAmut and BRCAwt patients with rEOC, but further phase III trial are needed in this setting.

Other intraperitoneal chemotherapy

A large case-control propensity-score study by Lu *et al.* (64) on 310 patients with rEOC compared CRS associated with platinum-based NIPEC with CRS associated with IV CT, showing significantly longer DFS in the NIPEC group, both in platinum-S and platinum-R patients (4.9 *vs.* 2.4 months, P<0.001, for platinum-R disease, and 9.8 *vs.* 6.9 months, P<0.001, for platinum-S disease). Three prospective observational studies (71-73) focusing on rEOC treated with PIPAC with cisplatin and doxorubicin showed a histologic tumor regression in 64% with median OS ranging from 13.6 to 14.7 months. The reported OS and DFS obtained with IP CT other than HIPEC in rEOC ranged from 13.6 to 25.5 months and from 2.4 to 9.8 months, respectively.

Consolidation intraperitoneal chemotherapy

Intraperitoneal chemotherapy has also been applied as consolidation treatment when patients present complete response to primary treatment (CRS and systemic chemotherapy) to reduce the chance of recurrence.

HIPEC

Several non-randomized reports (*Tables 9*,*10*) have investigated the use of second-look surgery with HIPEC as additional treatment following a complete response to frontline therapy. The median OS and DFS of patients with EOC treated with consolidation HIPEC ranges from 14 to 64.4 moths (5y-OS 70–84.21%) and from 13 to 18.5 months (5y-DFS 45–63%) respectively. Some case-control studies (105-107) compared consolidation HIPEC after CRS and post-operative systemic chemotherapy with no further therapies. In the study by Gori *et al.* (105) patients in the HIPEC group reached a median OS of 64.4 months (5y-OS 70%) and a 5y-DFS of 45% compared with 46.4 months (5y-OS 58%) and 0% in the control group. In the study by Kim *et al.* (106) patients in the HIPEC group showed significantly higher 8y-OS (84% *vs.* 25%, P=0.0004) and 8y-DFS (63% *vs.* 29%, P=0.027).

A relative advantage of HIPEC delivery at the time of consolidation is the potential for a reduction in the toxicity of associated CRS (29). The major morbidity associated

Table 9 Prospective observational studies focus on intraperitoneal chemotherapy as consolidation therapy for EOC

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO (Inclusion of persistent EOC[§]?)	IP therapy technique	no. of pts	Treatment and Chemotherapy regimen	Platinum-Sensitive pts	CC0-1 n (%)	Median OS (months) [5y-OS%]	Median DFS or PFS° (months) [5y-DFS%]	Morbidity (3-4 grade/ severe) %	Mortality %
Piccart (103)	2003	RCT	cEOC	IIB-IIC-III (no)	IP	76	CRS + Platinum-based IV CT with complete remission at surgical second-look + IP Cis 4 cycles	–	CC-0: 17 (22.3)	[70]	[52]	(15)	0
						76	CRS + Platinum-based IV CT with complete remission at surgical second-look + no further treatment		CC-0: 17 (22.3)	[60]	[52]	–	–
Pomel (98)	2010	Cohort	cEOC + rEOC	IIIC (yes)	HIPEC	31	CRS + post-op IV CT with Cis 6 cycles + second-look laparotomy + HIPEC with Oxa 460 mg/m^2	–	CC-0 31 (100)	[2y-OS 67%]	[2y-DFS 27%]	(29)	0
Tournigand (104)	2003	Cohort	cEOC	III-IV (yes)	EPIC	68	Exploratory laparotomy + IV CT with Cis and Anthracycline + second-look laparotomy (RT <1 cm) + post-op IP CT with Cis 100 mg/m^2 + VP16 150 mg/m^2 on day 1, Mitoxantrone 25 mg/m^2 on day 2	–	CC-0: 13 (19)	73 [58]	34 [34] No RT: 42 RT <2 cm: 40; RT >2 cm: 26	(51)	0

[§]EOC with sub-optimal cytoreduction at primary surgery and evidence of persistent peritoneal disease; RCT, randomized controlled trial; Cis, Cisplatin; Doxo, Doxorubicin; Oxa, Oxaliplatin; CT, chemotherapy; Ca-Co, case-control; rEOC, recurrent EOC; pEOC, primary EOC; cEOC, HIPEC for consolidation; NA, not available.

Table 10 Retrospective observational studies focusing on intraperitoneal chemotherapy as consolidation therapy for EOC

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO (Inclusion of persistent EOC[§]?)	IP therapy technique	no. of pts	Treatment and Chemotherapy regimen^	Platinum-Sensitive pts	CC0-1 n (%)	Median OS (months) [5y-OS%]	Median DFS or PFS° (months) [5y-DFS%]	Morbidity (3-4 grade/ severe) %	Mortality %
HIPEC													
Gori (105)	2005	Retrospective Case-control	cEOC	IIIB-IIIC (no)	HIPEC	Ca 32	CRS + post-op IV CT 6 cycles with Cis or cyclophosphamide + negative second-look laparotomy + HIPEC with Cis 100 mg/m^2	–	–	64.4 [70]	[45]	3.1 (3.1)	0
						Co 19	CRS + post-op IV CT 6 cycles with Cis or cyclophosphamide			46.4 [58]	[0]	–	
Kim (106)	2010	Retrospective Case-control	cEOC	Ic-IIIc (no)	HIPEC	Ca 19	CRS + post-op IV CT + negative second-look laparotomy + HIPEC with Paclitaxel 175 mg/m^2	–	–	Not reached [84.21] [8y-OS 84.21%]	Not reached [63.13] [8y-DFS 63.16%]	(36.8)	0
						Co 24	CRS + post-op IV CT + negative second-look laparotomy			51 [41.67] [8y-OS 25.0%]	18.5 [29.17] [8y-DFS 29.17%]		
Mendivil (107)	2017	Retrospective Case-control	cEOC	IIIA-IV (no)	HIPEC	Ca 69	CRS+ post-op IV CT with Carbo-Taxol + negative second-look VLS + HIPEC with Carbo (AUC 10) + post-op IV CT	–	–	Mean OS 33.8	Mean DFS 25.1	(0)	0
						Co 69	CRS + post-op IV CT with Carbo-Taxol			Mean OS 33.6	Mean DFS 20.0		

Table 10 (*continued*)

Table 10 (*continued*)

First authors (ref.)	Year	Case-control or cohort	Primitive/ Recurrence	FIGO (Inclusion of persistent EOC[§]?)	IP therapy technique	no. of pts	Treatment and Chemotherapy regimen^	Platinum-Sensitive pts	CC0-1 n (%)	Median OS (months) [5y-OS%]	Median DFS or PFS° (months) [5y-DFS%]	Morbidity (3-4 grade/ severe) %	Mortality %
Rettenmaier (108)	2015	Retrospective Cohort	cEOC	IC-IV (no)	HIPEC	37	CRS + post-op IV CT with Carbo-Taxol + HIPEC with Carbo (AUC 10) + IV CT with Taxol	–	–	14	13	(16.2)	0
Other intraperitoneal chemotherapy													
Suidan (109)	2014	Retrospective Case-control	cEOC	III-IV (no)	EPIC	Ca 62	CRS + post-op IV CT + second-look with consolidation IP CT with Cis 75 mg/m^2 3-5 cycles	–	CC-0: 34 (55)	57.5	19.7	–	–
						Co 162	CRS + primary post-op IV/IP CT: IV paclitaxel 135 mg/m^2 over 3 h on day 1, IP Cis 75 mg/m^2 on day 2, and IP Paclitaxel 60 mg/m^2 on day 8		CC-0: 100 (62)	78.8	23.7		
Mousavi (110)	2016	Retrospective Case-control	cEOC	II-IV (no)	EPIC	18 Ca	CRS + post-op IV CT with Carbo-Taxol + IP CT with Carbo 400 mg/m^2 for 3 cycles	–	–	39 [72.2]	13	5.6	0
						18 Co	CRS + post-op IV CT with Carbo-Taxol			30.8 [33.3]	9.5	–	–

[§]EOC with sub-optimal cytoreduction at primary surgery and evidence of persistent peritoneal disease; Cis, Cisplatin; Carbo, Carboplatin; cEOC, HIPEC for consolidation; CT, chemotherapy.

with consolidation HIPEC ranges from 0% to 51% and the mortality is 0% in all studies.

Other intraperitoneal chemotherapy

The RCT by Piccart on 152 patients with stage IIB-IIC-III EOC treated with CRS and platinum-based systemic CT with evidence of complete remission at surgical second-look, compared patients treated with post-operative consolidation NIPEC cisplatin (administered through an intraperitoneal catheter) with Cisplatin with patients treated with no further therapies. In the NIPEC group, the 5y-OS and 5y-DFS were 70% and 53% respectively, compared to 60% and 52% in control group. The respective hazard ratios for DFS and OS with 95% CI: were 0.89 (0.59-1.33) and 0.82 (0.52-1.29). For the NIPEC consolidation CT (other than HIPEC) median OS ranges from 39 to 73 months (5y-OS 58-72%) and median DFS from 13 to 34 months (5y-DFS 34-52%). Suidan *et al.* compared survival outcomes for patients with advanced EOC who received primary systemic and IP chemotherapy to those who received systemic CT followed by consolidation IP chemotherapy. In this study primary IP chemotherapy was associated with improved OS and with the same DFS compared to systemic CT followed by consolidation IP CT in patients with optimally cytoreduced advanced EOC (median OS 78.8 *vs.* 57.5 months, P=0.004; median DFS 23.7 *vs.* 19.7 months, P=0.11).

Early postoperative intraperitoneal chemotherapy (EPIC)

Early postoperative intraperitoneal chemotherapy (EPIC) presents some potential advantages in respect to the HIPEC (84,111). In fact, it is administered immediately after the CRS and inside the abdomen when the tumor burden within the abdominal cavity is minimal. EPIC timing and way of administration may allow an effective penetration within sites of wound healing potentially reducing the possibility to have cancer cells entrapped within fibrin deposits and scars.

EPIC associated potential disadvantages are the increased rate of postoperative morbidity and infections (112-114). EPIC does not necessitate hyperthermia and may be utilized after HIPEC or CRS alone. It is usually administered within the 4^{th}-5^{th} post-operative day through the abdominal drains placed during surgery. Therapy cycles usually last for 24 hours ensuring an adequate exposure of the tumor cells to the drugs. Suggested drugs for EPIC are the cell-cycle specific such as 5-fluorouracil and taxanes (115,116).

An alternative to EPIC is the dose-dense early postoperative intraperitoneal chemotherapy (DD-EPIC) given in front-line. It seems to give good results. In fact, some data showed that DD-EPIC seems to significantly increase non-progression rate in advanced OC. A phase 2 trial where 218 patients with FIGO IIIC–IV OC were randomly allocated to receive DD-EPIC followed by intravenous (IV) chemotherapy (DD-EPIC group), or IV chemotherapy alone (IV group) reported a median OS of 67.5 and 46.3 months in the DD-EPIC and IV group, respectively. Estimated OS at 5 years was 61.0% with DD-EPIC, and 38.2% with IV. Estimated PFS at 5 years was 26.0% *vs.* 8.5% for DD-EPIC and intravenous, respectively (117).

Intraperitoneal drugs in ovarian cancer:

Several drugs have been utilized intraperitoneally in treating EOC. Dosages, perfusion times, and methodologies are different across the different centers. Even if supported by definitive scientific literature, most of these drugs have never been recognized as officially applicable within the peritoneal cavity. In several cases the use of IP drugs for HIPEC, EPIC or NIPEC administration is off-label under the direct responsibility of the oncologists and surgeons.

Cisplatin (cis-diamminedichloroplatinum-III, CDDP) action works through the formation of adducts to DNA causing cells apoptosis (118). CDDP can be applied in normothermia or in hyperthermia. Hyperthermia seems to augment the CDDP effect (119-121). The main concern in CDDP use is the potential nephrotoxicity (122). However, it has been questioned if the potential nephrotoxicity is mainly due to the renal excretion and the consequent potential toxicity, or to the fact that surgical physiological load of extensive CRS on already unhealthy kidneys may promote a secondary-hit related renal injury leading to renal insufficiency (123). This may necessitate, in the most severe cases, transient or definitive renal replacement therapy. The toxicity, in fact, seems to be related to the aggressive CRS and not only to drug exposure (95). Renal failure is generally relatively low and under the toxicity threshold (95). Moreover, the broad heterogeneity in the CDDP dosages throughout the different trials is not correlated to the different complication rates, further suggesting the correlation of the complications rate to the CRS procedure

and not only to the CDDP administration.

Taxanes act by stabilizing the microtubule against depolymerization thereby disrupting normal microtubule dynamics and preventing the cells to perform their normal activity in a cell cycle-specific way (124). The main characteristic of paclitaxel and docetaxel is the high molecular weight that allows for a high area under the curve (AUC) ratio of 853 and 861, respectively (125). This characteristic contributes to give to these drugs a clear pharmacokinetic advantage for IP administration (126). Conflicting results exist about the possible thermal augmentation of this class of drugs (126). Taxanes have been used in a neoadjuvant intraperitoneal setting as well as EPIC or adjuvant post-operative repetitive administrations. The research interest is to increase their bioavailability.

Doxorubicin or hydroxyldaunorubicin (adriamycin) is part of the antibiotic family of chemotherapy agents and precisely an anthracycline. It acts depending on the temperature modifying the cell membrane (127,128). Doxorubicin has a favorable AUC ratio of 230 due to the high molecular weight (129-133). The toxicity encountered in intravenous administration is a dose limiting cardiotoxicity that is not present with IP delivery. A mild thermal augmentation has been demonstrated for doxorubicin (134). PEGylated liposomal doxorubicin seems to have even more favorable pharmacokinetic effect (135).

Mitomycin C acts by cross-linking DNA with the antibiotic type molecule. It needs to be activated to enter the cells and be effective (136). Its AUC is 23.5 and this quality associated with thermal enhancement give the molecule a favorable action in HIPEC administration (137).

Oxaliplatin (oxalato-1,2-diaminocyclohexane-platinum (II)) has a very low AUC and a rapid absorption into the tissues. For these reasons oxaliplatin is usually administered during HIPEC with short application times. Hyperthermia enhance its effect on tumor cells but oxaliplatin-based HIPEC increase the risk of bleedings (119,138). In general, oxaliplatin should be infused within a dextrose-based carrier because of instability in other solutions (139).

Convincing data exist concerning the synergism between heat and the activity of many antineoplastic drugs against tumor cells growing *in vitro* (91,119). Pharmacokinetic data provide a credible rationale for HIPEC. However more data about the different pharmacological aspects and comparative efficacy studies between the different drugs are needed (98,112,140). The pharmacokinetics of several antineoplastic drugs utilized during HIPEC have been defined (61,116) especially for cisplatin (63) and paclitaxel, which are among the most effective against EOC. Good results have been demonstrated with the administration of the two drugs together during HIPEC (28,95,96). A comparable concentration of cisplatin + paclitaxel in the peritoneal tissue and in the perfusate during HIPEC have been demonstrated, showing a good antineoplastic effect with low systemic drug absorption. This will give the maximal anticancer effect with low risk of side-effects due to systemic drug circulation (95). However, the pharmacokinetics of these molecules was investigated during and after intraperitoneal administration with hyperthermia only when infused alone and not in combination. It is not possible to exclude pharmacokinetic interaction between these two different drugs. Some studies are trying to compare the effect of the different molecules when administered intraperitoneally with hyperthermia.

A prospective cohort of 41 patients with stage IIIC or IV EOC treated with CRS and HIPEC, where analyzed according to the two combinations of drugs. Cisplatin/doxorubicin were given to 19 patients (46%) and paclitaxel to the other 22 patients (54%). No difference in morbidity and mortality rate and survival rates were demonstrated within the two groups. The 3y-OS was 66% in cisplatin + doxorubicin group and 82.9% in paclitaxel group (P=0.248) (141).

Results

Present study included 57 patients: 35 with pEOC and 22 with rEOC. Three of the 35 patients with pEOC were treated with upfront CRS+HIPEC, while 32 with interval CRS+HIPEC. Pre-operative and intra-operative data are showed in *Table 11*. Mean PCI was 11.93±9.18. In the 89.5% of patients CC-0 was obtained. The 84.2% of patients received Cisplatin + Taxol as HIPEC regimen. Major complication rate and mortality rate were 35.1% and 1.8% respectively. Re-operation rate was 12.3%. The mean ICU length of stay (LOS) was 4.25 days (SD 9.7, median 2, range 0–54). The mean total LOS was 27.18 days (SD 24.00, median 20, range 10-124). The 70.2% of patients received post-operative IV CT. The mean OS for pEOC was 40.2 months (SE 3.9, 95% CI: 32.5–47.9). The median OS for pEOC was not reached. The median DFS for pEOC was 13 months (SE 1.7, 95% CI: 9.7–16.3), with 2y-OS of 71% and 2y-DFS of 37%. The median OS and DFS for rEOC were 46 months (SE 0.0) and 11 months (SE 2.9, 95% CI: 5.2–16.7) respectively, with 2y-OS of 68% and 2y-DFS of 34%. There was no significant difference in OS

Table 11 Patients' characteristics

Characteristics	n (%) or mean ± SD/median (min, max)
Primary EOC	35 (61.4)
Upfront CRS + HIPEC	3 (5.3)
Interval CRS + HIPEC	32 (56.1)
Recurrent EOC	22 (38.6)
Platinum-sensitive	7 (12.3)
Missing	15 (26.3)
FIGO stage	
IIIC	46 (80.7)
IV	10 (17.5)
Missing	1 (1.8)
Grading	
G1	2 (3.5)
G2	5 (8.8)
G3	44 (77.2)
Missing	6 (10.5)
BRCA status	
BRCA wild type	11 (19.3)
Missing	46 (80.7)
Histology	
Epithelial adenocarcinoma NOS	5 (8.8)
Serous adenocarcinoma	44 (77.1)
Clear-cell adenocarcinoma	1 (1.8)
Endometrioid carcinoma	6 (10.5)
Mucinous adenocarcinoma	1 (1.8)
PCI	
PCI <15	36 (63.2)
PCI ≥15	20 (35.1)
Missing	1 (1.8)
CC	
CC-0	51 (89.5)
CC-1 and CC-2	6 (10.5)
HIPEC regimen	
Cisplatin + Taxol	48 (84.2)
Cisplatin + Mitomycin	2 (3.5)
Cisplatin + Doxorubicin	5 (8.8)
Cisplatin alone	2 (3.5)
Pre-HIPEC chemotherapy regimen	
Primary EOC (n=35)	
NACT	30 (85.7)
Carboplatin + Taxol	2 (5.7)
Carboplatin + Taxol + Bevacizumab	
No NACT	3 (8.6)
In recurrent EOC (n=22) (more than one regimen for each patient)	
Carboplatin + Taxol	16 (72.7)
Bevacizumab	5 (22.7)
Niraparib	1 (4.5)
Doxorubicin	6 (27.3)
Trabectedin	3 (13.6)
Gemcitabine	2 (9.0)
Etoposide	1 (4.5)
Age	58.33±8.64/59 (42–73)
PCI	11.93±9.18/12 (0–37) (IQR 15)

and DFS between pEOC and rEOC (*Figure 2*).

No significant difference in OS and DFS was found between patients with FIGO stage IIIC and IV.

Among patients with rEOC, CC-0 patients had significantly longer median OS than CC-1,2 patients (46 *vs.* 4 months, P<0.001) with 2y-OS of 76% *vs.* 0%. Furthermore, patients with rEOC and PCI <15 had significantly longer median OS than patients with PCI>14 (46 *vs.* 19 months, P=0.014) with 2y-OS of 100% *vs.* 29%. *Tables 12* reports univariate and multivariate analysis of factors influencing OS. Cisplatin + Taxol as IP CT regimen

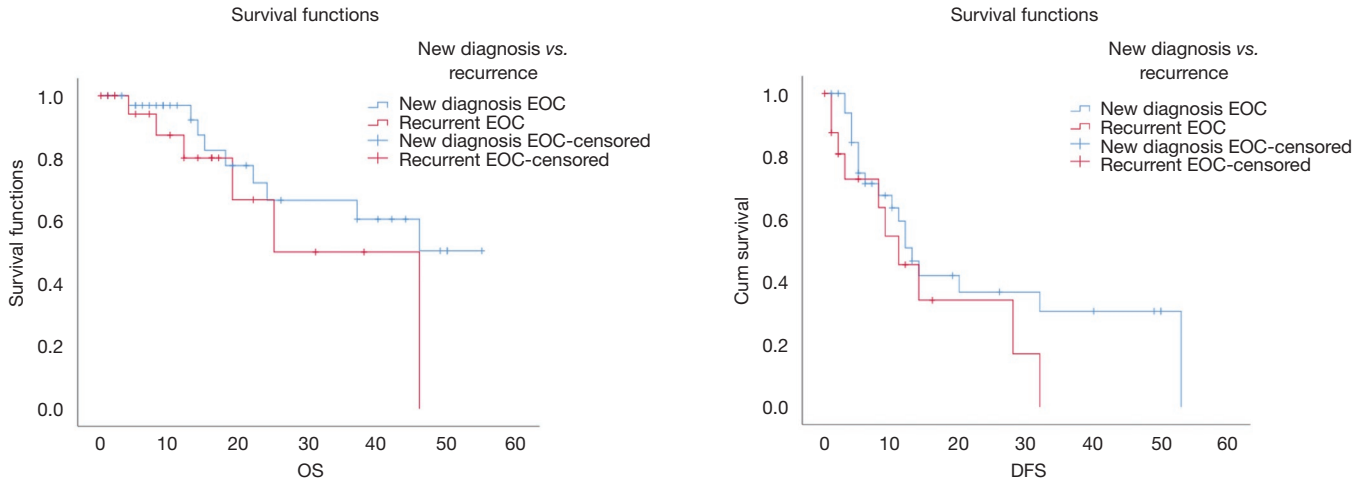

Figure 2 Kaplan-Meier survival curves of primary and recurrent epithelial ovarian cancer.

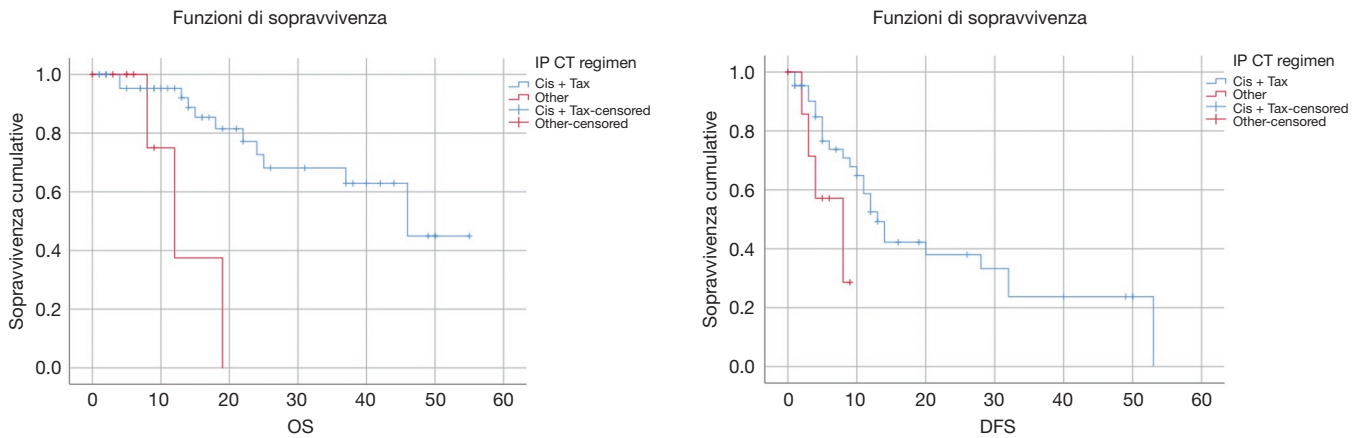

Figure 3 Kaplan-Meier survival curves of HIPEC cisplatin + paclitaxel *vs.* other HIPEC regimens.

was the only significant factor improving OS at multivariate analysis (OR 6.54, 95% CI: 1.24–34.47, P=0.027). Patients treated with IP Cisplatin + Taxol showed a median OS of 46 months (SD 6.4, 95% CI: 33.4–58.6), while patients treated with other IP regimens showed a median OS of 12 months (SD 3.1, 95% CI: 6.0–18.0). The 2y-OS was 72% and 3y-OS was 68% for Cisplatin + Taxol as IP CT, while the 2y and 3y-OS was 0% for other IP CT regimen (*Figure 2*).

Patients treated with IP Cisplatin + Taxol showed a median DFS of 13 months (SD 1.6, 95% CI: 9.9–16.1), while patients treated with other IP regimens showed a median DFS of 8 months (SD 3.1, 95% CI: 1.9–14.1) (*Figure 3*). Only tumor grading was the significant factor affecting DFS at univariate analysis (*Table 12*).

Conclusion

Intraperitoneal chemotherapy in ovarian cancer showed positive results that may be considered semi-definitive according to the level of evidence and should be maintained as a starting point for further investigations. At present intraperitoneal chemotherapy should be proposed to patients with advanced ovarian cancer as standard treatment at almost all disease stages. Platinum + taxane-based intraperitoneal regimens demonstrated superior results compared to other regimens.

Table 12 Univariate and multivariate analysis on risk factors for OS and DFS

Variables	Subgroups	Univariate analysis							Multivariate analysis		
		Mean	SD	95% CI	Median	SD	95% CI	P value	P value	OR	95% CI: OR
Overall survival											
New diagnosis *vs.* recurrent EOC	New diagnosis EOC	40.2	3.9	32.5–47.9	–	–	–	0.266	–	–	–
	Recurrent EOC	31.4	5.5	20.6–42.2	46.0	0.0	–		–	–	–
FIGO	IIIC	38.5	3.7	31.1–45.8	46.0	15.8	14.9–77.1	0.690	–	–	–
	IV	34.5	6.3	22.0–46.9	46.0	23.4	0.07–91.9		–	–	–
Grading	G1	12.0	0.0	12.0–12.0	12.0	–	–	0.007	0.183	Ref	Ref
	G2	25.0	12.0	1.5–48.5	13.0	–	–		0.926	1.15	0.06–21.82
	G3	39.1	3.6	32.1–66.1	46.0	15.0	16.5–75.5		0.371	0.31	0.025–3.98
IP CT regimen	Cis + Tax	40.3	3.3	33.9–46.8	46.0	6.4	33.4–58.6	0.002	0.027	6.54	1.24–34.47
	Other	13.6	3.0	7.7–19.5	12.0	3.1	6.0-18.0				
CC	CC-0	39.2	3.5	32.3–46.1	46.0	–	–	0.160	–	–	–
	CC-1.2	27.5	12.0	3.9–51.0	46.0	0.0	–		–	–	–
Pre-operatory CT	No	Not calculated because all cases are censured						0.691			
	Yes										
Adjuvant CT	No Adjuvant CT	27.9	6.0	16.2–39.6	24.0	4.2	15.7–32.3	0.166	–	–	–
	Adjuvant CT	40.9	3.6	33.8–47.9	46.0	5.5	35.3–56.7		–	–	–
PCI	PCI <15	40.9	3.5	34.0–47.9	46.0	–	–	0.102	–	–	–
	PCI ≥15	27.5	5.3	17.1–37.8	22.0	2.9	16.2–27.8		–	–	–
	Continuous variable	OR 1.07						0.064			
AGE	Age <60	39.8	4.0	31.9–47.6	46.0	13.9	18.8–73.2	0.470	–	–	–
	Age ≥60	32.0	5.1	22.0–42.1	37.0	10.2	16.9–57.1		–	–	–
	Continuous variable	OR 1.02						0.534	–	–	–

Table 12 (*continued*)

Table 12 (*continued*)

Variables	Subgroups	Univariate analysis							Multivariate analysis		
		Mean	SD	95% CI	Median	SD	95% CI	P value	P value	OR	95% CI: OR
Disease-free survival											
New diagnosis *vs.* recurrent EOC	New diagnosis EOC	23.8	4.2	15.5–32.2	13.0	1.7	9.7–16.3	0.206	–	–	–
	Recurrent EOC	14.9	3.6	7.9–21.9	11.0	2.9	5.2–16.8		–	–	–
FIGO	IIIC	21.9	4.0	14.0–29.7	13.0	1.8	9.4–16.6	0.731	–	–	–
	IV	19.0	5.7	7.9–30.2	12.0	2.7	6.7–17.3		–	–	–
Grading	G1	2.5	0.5	1.5–3.5	2.0	/	/	<0.001	–	–	–
	G2	11.3	1.9	7.6–15.1	13.0	0.0	/		–	–	–
	G3	20.6	3.5	13.7–27.5	12.0	1.6	8.8–15.2		–	–	–
IP CT regimen	Cis + Tax	22.4	3.5	15.5–29.3	13.0	1.6	9.9–16.1	0.091	–	–	–
	Other	6.1	1.1	4.1–8.2	8.0	3.1	1.9–14.1		–	–	–
CC	CC-0	21.1	3.4	14.4–27.8	12.0	1.7	8.7–15.3	0.935	–	–	–
	CC-1.2	15.4	5.1	5.4–25.4	12.0	8.2	0.0–28.0		–	–	–
Pre-operatory CT	No	Not calculated because all cases are censured						0.274			
	Yes										
Adjuvant CT	No	18.1	6.5	5.3–30.9	10.0	3.4	3.3–16.7	0.591	–	–	–
	Yes	21.9	3.8	14.4–29.3	13.0	1.4	10.2–15.8		–	–	–
PCI	PCI <15	24.7	4.1	16.7–32.8	14.0	5.2	3.7–24.3	0.066	–	–	–
	PCI ≥15	10.0	1.7	6.7–13.3	10.0	1.5	7.1–12.9		–	–	–
	Continuous variable	OR 1.04 (95% CI: 0.99–1.09)						0.092			
AGE	Age <60	20.2	4.0	12.4–28.1	12.0	2.2	7.7–16.3	0.771	–	–	–
	Age ≥60	24.4	5.2	14.2–35.0	12.0	1.6	8.9–15.2		–	–	–
	Continuous variable	OR 1.01 (95% CI: 0.97–1.06)						0.539	–	–	–

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Footnote

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