Heated IntraPEritoneal Chemotherapy (HIPEC) for Patients With Recurrent Ovarian Cancer

A Systematic Literature Review

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Background: Despite advances in surgical oncology, most patients with primary ovarian cancer develop a recurrence that is associated with a poor prognosis. The aim of this review was to establish the impact of Heated IntraPEritoneal Chemotherapy (HIPEC) in the overall survival of patients with recurrent ovarian cancer.

Methods: A search of PubMed/MEDLINE databases was performed in February 2015 using the terms "recurrent ovarian cancer," "cytoreductive surgery/cytoreduction," and "heated/hyperthermic intraperitoneal chemotherapy." Only English articles with available abstracts assessing the impact of HIPEC in patients with recurrent ovarian cancer were examined. The primary outcome measure was overall survival, whereas secondary outcomes included disease-free survival and HIPEC-related morbidity.

Results: Sixteen studies with 1168 patients were analyzed. Most studies were Level IV, with 4 studies graded as Level III and 1 Level II. Cisplatin was the main chemotherapeutic agent used, but variations were observed in the actual technique, temperature of perfusate, and duration of treatment. In patients undergoing cytoreductive surgery and HIPEC, the overall survival ranged between 26.7 and 35 months, with disease-free survival varying between 8.5 and 48 months. Heated IntraPEritoneal Chemotherapy seems to confer survival benefits to patients with recurrent disease, with a randomized controlled study reporting that the overall survival is doubled when cytoreductive surgery is compared with cytoreductive surgery and chemotherapy (13. 4 vs 26.7 months). Heated IntraPEritoneal Chemotherapy–related morbidity ranged between 13.6% and 100%, but it was mainly minor and not significantly different from that experienced by patients who only underwent cytoreduction.

Conclusions: Cytoreductive surgery and HIPEC seem to be associated with promising results in patients with recurrent ovarian cancer. Large international prospective studies are required to further quantify the true efficacy of HIPEC and identify the optimal treatment protocol for a maximum survival benefit.

Key Words: Recurrent ovarian cancer, Heated IntraPEritoneal Chemotherapy, HIPEC

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Ovarian cancer accounts for more deaths than any other gynecological malignancy. Approximately 225,000 new cases are diagnosed every year worldwide, with an annual death rate of 140,000.[1] In the United Kingdom alone, it is the fifth most common cancer in females, with an annual incidence of 5984 cases[2] and 3568 deaths.[3] In the United States, more than 15,000 women die every year from the disease. Recent population-based studies have indicated a 5-year age-standardized relative survival of 31% in the United Kingdom compared with a European rate of 37%.[4] The low survival rate is caused by the nonspecific initial presentation of the disease and its propensity for peritoneal spread, with approximately two thirds of patients diagnosed with advanced stage III or IV disease.[5]

Current treatment options for primary ovarian cancer involve the use of maximum cytoreductive surgery (CRS) and systemic platinum-based chemotherapy. This approach has extended the median survival time to more than 4 years, but no change has been achieved in overall survival during the last 3 decades.[6] Although 70% to 80% of patients respond to initial therapy, typically, only 15% are cured, with the remaining developing drug-resistant recurrent disease.[7–10] The median survival of patients with recurrent ovarian cancer ranges between 12 and 24 months.[7] Therefore, one of the ongoing clinical challenges is to develop new therapies and treatment strategies for patients with recurrent disease.

Recently, the use of Heated IntraPEritonal Chemotherapy (HIPEC) has been proposed in view of promising Level I[11–13] and Level III[14–16] evidence, demonstrating its benefits in patients with other abdominal malignancies (eg, advanced colon or gastric cancer). Furthermore, bidirectional chemotherapy using intravenous paclitaxel or ifosfamide and intraperitoneal cisplatin and paclitaxel seems to improve the survival of patients with stage III primary ovarian malignancies.[17,18]

The aim of this systematic review was to evaluate current evidence for the use of CRS and HIPEC in the treatment of patients with recurrent ovarian cancer. The primary outcome measure of this study was overall survival, whereas secondary outcomes were defined as disease-free survival (DFS) and HIPEC-related morbidity.

METHODS

A search of PubMed and MEDLINE databases was performed in February 2015 to identify all studies investigating the outcome of CRS with HIPEC for recurrent ovarian cancer. A clinical trial database (www.clinicaltrials.gov) was also searched for randomized controlled trials. The search strategy included the text terms "recurrent ovarian cancer," "cytoreductive surgery/cytoreduction," "hyperthermic/Heated IntraPEritoneal Chemotherapy," and "HIPEC." The key words were used in all possible combinations to extract the maximum number of articles. The search strategy was restricted to articles written in English, with available abstracts, between 1980 and 2015. If multiple studies from the same institution were identified, the most recent study with the longest follow-up was included in the analysis. Furthermore, if an abstract or full article was determined as being irrelevant (eg, primary ovarian cancer, mixed cohort with primary and recurrent disease not performing subgroup analysis, study not assessing the effect of HIPEC), it was excluded from the final analysis. Selected articles were additionally cross referenced by hand. A diagrammatic illustration of the search process is shown in Figure 1.[19–52] Two reviewers (A.H. and D.D.) qualitatively assessed all studies using the Oxford Centre for Evidence-Based Medicine 2011 levels of evidence. Any disagreements were settled by consensus.

RESULTS

An initial literature search yielded 50 potential studies for review. After applying the inclusion and exclusion criteria, 16 studies were identified that were eligible for analysis (Fig. 1). They included 1168 patients with recurrent ovarian cancer who underwent CRS, of which 81.6% (n = 953) received HIPEC. Eleven studies were Level IV, with 4 graded as Level III and 1 as Level II (Table 1). On initial assessment, wide variations were observed in the choice of HIPEC drug regimen and technique (ie, temperature of perfusate, duration, and open or closed technique).

Choice of HIPEC Drugs/Regimen

Fourteen studies included 1 platinum-based agent (cisplatin, oxaliplatin, or carboplatin). Eight studies[53–56,72–75] used these drugs in isolation. Piso et al[75] used either cisplatin or mitoxantrone but did not elaborate further as to how many patients received each drug. In the largest multicenter study,[76] with N = 474 patients, cisplatin was the most commonly used agent (75%) either on its own or in combination with mitomycin or doxorubicin. Five studies[77–81] used cisplatin with doxorubicin,[77,79,80] paclitaxel,[78] or mitomycin.[79–81] Three studies used oxaliplatin,[56,72,73] with only 1 study electing to use it in combination (with irinotecan in some patients). Spiliotis et al[78] used a combination of doxorubicin, paclitaxel, and mitomycin to treat a subgroup of patients who were platinum resistant. Finally, 2 studies[82,83] reported the use of paclitaxel at a dose of 60 mg/m^2 for 60 minutes at 41°C to 43°C.[75]

Cisplatin Group

Eleven studies used cisplatin with doses ranging from 20 to 250 mg/m^2. Bakrin et al[76] used 50 mg/m^2, and most studies used a dose between 50 and 100 mg/m^2. Only Ceelen et al[73] used a higher dose (100–250 mg/m^2), whereas the lowest dose (20 mg/m^2) was used by Cotte et al.[74] Infusion time was varied between 60[77,78,81] and 120 minutes[73–76,79,80]; in addition, the target temperatures of the perfusate varied between 40.5°C[73] to as high as 46°C.[74]

Oxaliplatin Group

Three studies used oxaliplatin to treat 54 patients.[56,72,73] Two studies used this in isolation; a dose of 460 mg/m^2 was used with an infusion time of 30 minutes. The target temperatures of the perfusate were close to 40.5°C[73] and 41.5°C.[72] The third study[56] used oxaliplatin (460 mg/m^2) or oxaliplatin (360 mg/m^2) and irinotecan (360 mg/m^2) with an infusion time of 30 minutes at 43°C.

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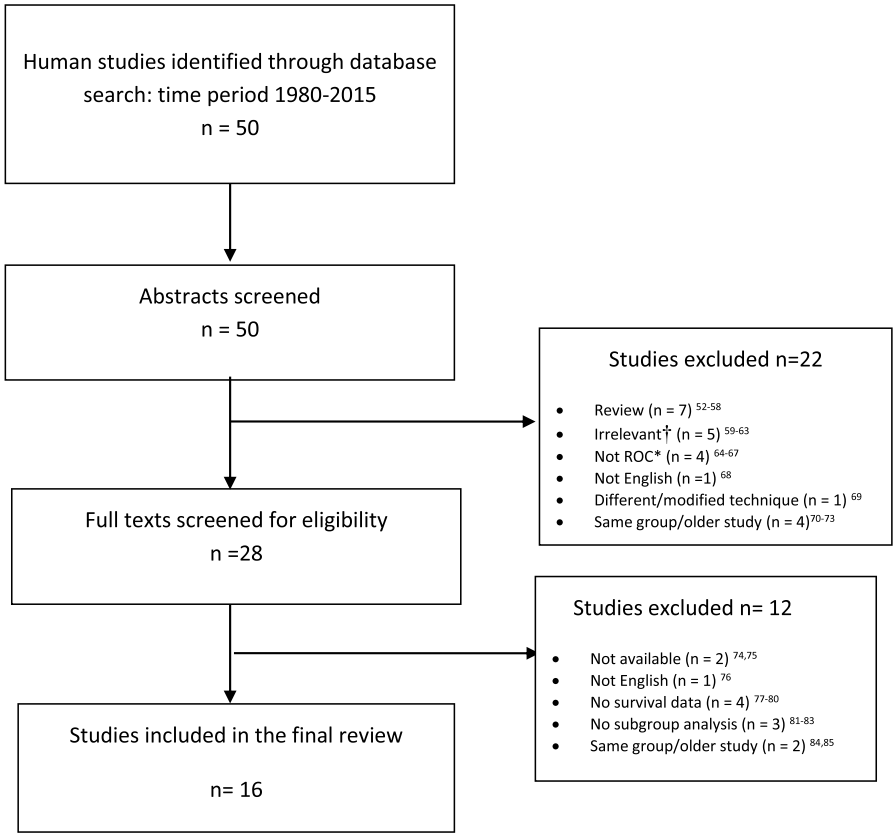

FIGURE 1. Diagrammatic illustration of the search strategy. *ROC, recurrent ovarian cancer. †No survival data, no subgroup analysis. RCT, randomized controlled trial; CRS, cytoreductive surgery; HIPEC, Heated IntraPEritoneal Chemotherapy; OS, overall survival; DFS, disease-free survival.

Carboplatin Group

Two studies used carboplatin.[55,79] One study used it in isolation to treat 10 patients at a dose of 1000 mg/m^2 for 90 minutes at 40 to 43°C.[55] The second study used carboplatin with paclitaxel 60 mg/m^2 for 120 minutes at 42.5°C to treat an undisclosed number of patients.[79]

Paclitaxel Group

Two studies used paclitaxel at 60 mg/m^2 as the sole HIPEC agent.[82,83] The temperature of the perfusate was similar in both studies, ranging between 41°C and 43°C. However, 1 study used an infusion time of 60 minutes[83]; whereas in the second, no infusion time is reported.[82] In addition, paclitaxel was used in 2 other studies in combination with cisplatin[78] and carboplatin.[79]

Platinum-Resistant Group

Only 1 study[78] reported the use of an alternative regimen for platinum-resistant cases: doxorubicin 35 mg/m^2 was used in conjunction with either paclitaxel 175 mg/m^2 or mitomycin 15 mg/m^2 in n = 26 patients compared with cisplatin 100 mg/m^2 and paclitaxel 175 mg/m^2 for platinum-sensitive cases (n = 34). In addition, Deraco et al[80] made reference to 2 patients who were treated with doxorubicin for platinum-resistant disease.

Open Versus Closed Technique

Heated IntraPEritoneal Chemotherapy is usually performed using an open or closed technique. In the former, the edges of the incision are elevated, creating an intraperitoneal reservoir into which the inflow and outflow lines carry the heated chemotherapy solution. In the latter, the abdominal wall is temporary closed and the inflow and outflow lines are placed into the abdominal cavity via separate incisions. Benefits of the open method include a better distribution of the heat and chemotherapy solution through the abdomen and pelvis compared with the closed method where heat loss is minimized, allowing better maintenance of the hyperthermic state.[84]

Five hundred and eighty (60.9%) HIPEC procedures were performed using the open method, whereas 324 (39.1%) were carried out using the closed technique. All studies used

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TABLE 1. Summary of studies investigating the use of HIPEC in patients with recurrent ovarian cancer

Author	Year	No.	Age, y	Design (Level of Evidence)	HIPEC Drugs
Delotte	2015	15	72[37–44]	Single-center retrospective Level IV CRS + HIPEC	Cisplatin (50 mg/m^2) and doxorubicin (15 mg/m^2) for 60 min at 43.0°C
Cascales-Campos	2015	Total: 54 HIPEC: 32 Non-HIPEC: 22	HIPEC: 54[19–45,57–68] Non-HIPEC: 55[19–40,57–71]	Case control Level III CRS + HIPEC + chemo CRS + chemo	Paclitaxel 60 mg/m^2 at 42°C
Spiliotis	2014	Total: 120 HIPEC: 60 Non-HIPEC: 60	HIPEC: 58.3 Non-HIPEC: 58.1	RCT Level 2 CRS + HIPEC + chemo CRS + chemo	Platinum sensitive: cisplatin 100 mg/m^2 + paclitaxel 175 mg/m^2 for 60 min at 42.5°C Platinum resistant: doxorubicin 35 mg/m^2 + paclitaxel 175 mg/m^2 or mitomycin 15 mg/m^2 for 60 min at 42.5°C
Safra	2014	Total: 111 HIPEC: 27 Non-HIPEC: 84	HIPEC: 54.3 Non-HIPEC: 54.3	Case control Level 3 CRS + HIPEC systemic chemo	Cisplatin 50 mg/m^2 + doxorubicin 15 mg/m^2 or paclitaxel 60 mg/m^2 + carboplatin (AUC-4) or cisplatin 25 mg/L per m^2 + mitomycin-C 3.3 mg/L per m^2 for 120 min at 42.5°C
Königsrainer	2014	90	55[18–43,53–85]	Single center, retrospective, Level IV	Cisplatin 50 mg/m^2 for 90 min at 42.0°C
Zivanovic	2014	12	54[19–37,57–68]	Single-center prospective cohort Level IV	Cisplatin at either 60 mg/m^2 (n = 3), 80 mg/m^2 (n = 33) or 100 mg/m^2 (n = 6) for 90 min at 41°C–43°C
Bakrin	2013	474	57.4 (22.6–77.6)	Multicenter, retrospective, Level IV	Cisplatin was the most commonly used drug(75%) at a dose of 50 (30–100) mg/m^2 for 90 (30–120)min at 42°C[15–18,53–62,69–85]
Argenta	2013	10	56[19–33,64–68]	Prospective cohort Level IV	Carboplatin 1000 mg/m^2 for 90 min at 40°C–43°C
Gouy	2013	7	53[19–28,57–71,76–85]	Retrospective cohort Level IV	Oxaliplatin 460 mg/m^2 or oxaliplatin 360 mg/m^2 + irinotecan 360 mg/m^2 for 30 min at 43°C
Fagotti	2012	Total: 67 HIPEC: 30 Non-HIPEC: 37	HIPEC: 51[19–30,58–68] Non-HIPEC: 55[19–36,57–71,81–85]	Case control Level III CRS + HIPEC CRS + chemo	Oxaliplatin 460 mg/m^2 for 30 min at 41.5°C
Deraco	2012	56	55.2[19–42,57–71,79–85]	Cohort Level IV CRS+ HIPEC + chemo	Cisplatin (42 mg/L) + doxorubicin (15 mg/L) in 4–6 L perfusate or cisplatin (25 mg/L per m^2) + mitomycin-C (3.3 mg/L per m^2) for 90 min at 42.5°C
Ceelen	2012	42	54[19–38,56–85]	Cohort Level IV Pretreated + CRS + HIPEC + chemo	Cisplatin (100–250 mg/m^2) for 90 min or xalioplatin (460 mg/m^2) for 30 min at 40.5°C–41°C
Roviello	2010	8	56[19–39,57–71,77–85]	Single-center cohort Level IV CRS + HIPEC	Cisplatin (100 mg/m^2) and mitomycin C (25 mg/m^2) for 60 min at 41°C–43 °C
Muñoz-Casares	2009	Total = 26 HIPEC = 14 Non-HIPEC = 12	HIPEC: 54[19–35,57–71,77–85] Non-HIPEC: 54[19–34,57–71,79–85]	Single-center, nonrandomized case-controlled Level III CRS + HIPEC + Chemo CRS + chemo	Paclitaxel(60 mg/m^2) for 60 min at 41°C–43 °C
Cotte	2007	65	54.3[19–42,57–71,79–85]	Cohort Level IV CRS + HIPEC + chemo	Cisplatinum 20 mg/m^2 for 90 min at 44°C–46°C
Piso	2004	11	54[19–46,57–71,85]	Single-center cohort Level IV CRS + HIPEC ± chemo	Mainly cisplatin at a dose of 75 mg/m^2 for 90 min at 41.5 °C

CC, completeness of cytoreduction; OS, overall survival; PCI, Peritoneal Carcinomatosis Index.

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PCI	CC	Technique (Open or Closed)	OS	DFS	Morbidity
11[3–18,53–56]	CC-0 = 60% CC-1 = 40%	Open	Median OS: 35 (28-not reached) mo	15.6 mo (median)	20% grade III or IV complications
HIPEC: 8[2–18,53–56,72] Non-HIPEC: 4[2–16]	CC-0 = 54	Open	N/A	At 3 y: HIPEC: 45% Non-HIPEC: 23%	HIPEC: 28% (21% grade III/I) Non-HIPEC: 23% (14% grade III/IV)
HIPEC: 48% ≥10 Non-HIPEC: 50% ≥10	HIPEC: CC-0 65% Non-HIPEC: CC-0 55%	Open: 40 Closed: 20	HIPEC mean OS: 26.7 mo Non-HIPEC mean OS: 13.4 mo Platinum sensitive HIPEC mean OS: 26.8 mo Platinum sensitive non-HIPEC mean OS: 15.2 mo	N/A	N/A
N/A	N/A	Closed	At 5 y HIPEC: 79% Non-HIPEC: 43%	HIPEC: 15 mo (median) Non-HIPEC: 6 mo (median)	All patients experienced mild electrolyte abnormalities
20[3–18,53–56,69–85]	CC-0 = 52% CC-1 = 17% CC-2 = 6% CC-3 = 25%	Open	Median OS CC-0/1 = 35 (95% CI 23–46) mo Median OS CC–2/3 = OS 14 (95% CI 4–25)	NA	42% overall complication rate (grades I-IV)
15.5[4–18,53–56,72–77]	CC-0: 58% CC-1: 8% CC-2: 34%	Closed	At median follow-up of 20.6 mo (13.9–27.6), OS = 66.6%	13.6 mo (median)	25% (severe)
0–8 (52%) > 8 (48%)	CC-0 = 75% CC-1,2,3 = 25%	Open: 329 Closed: 145	Median OS = 45.7 mo Year 1 survival rate = 89% Year 3 survival rate = 59% Year 5 survival rate = 37%	NA	No subgroup analysis for patients with recurrent disease but grade III and IV complications in 30% of procedures performed for advanced and recurrent disease
N/A	CC-0: 6 CC-1: 4	Closed	At median follow-up of 16 mo,[5–18,53–56,72] OS = 90%	At median follow-up of 16 mo[5–18,53–56,72]: 70%	30% grade III/IV
N/A	CC-0: 7	Open	At median follow-up of 32 mo,[19–23,57–71,74–85] OS = 100%	At median follow-up of 32 mo[19–23,57–71,74–85]: 28.6%	All patients experienced early grade II/III14% grade III
HIPEC: CC-0 = 96.7% CC-1 = 3.3% Non-HIPEC – all CC-0	HIPEC: all CC-0 Non-HIPEC: CC-0 = 96.7% CC-1 = 3.3%	Closed	HIPEC 5-yr OS: 68.4% Non-HIPEC 5-y OS: 42.7%	HIPEC (45 mo median follow-up): 33.3% Non-HIPEC (36 mo median follow-up: 0%	N/A
15.2[4–18,53–56,72–79] (median)	CC-0 = 47 CC-1 = 7 CC-2 = 1 Unknown = 1	Closed	5-yr OS: 23% Median OS: 25.7 mo	At 5 y: 7%	26.3% (severe) 5.3% procedure-related mortality
4[2–7] (median)	CC-0 = 50% CC-1 = 36% CC-2 = 14%	Open	5-y OS: 41.3% Median OS: 37 mo	At 5 y: 12.5%	21% major
PCI 1–6 (87.5%) PCI > 15 (12.5%)	CC-0 = 75% CC-1 = 25%	Closed	5-y survival probability = 44% ± 22%	N/A	Grade III/IV complications in 12%
HIPEC = 13 ± 6 Non-HIPEC = 13 ± 6	CC-0 HIPEC = 64% Non-HIPEC = 58%	Open	5-y OS HIPEC = 57% Non-HIPEC = 17%	HIPEC = 48 ± 42 mo Non-HIPEC = 24 ± 18 mo	HIPEC = 29% Non-HIPEC = 25% Mainly grade I and II
N/A	N/A	Closed	Median OS: 28.4 mo	8.5 mo (median)	13.6% major
NA	N/A	Open	Mean OS = 30 ± 6 mo	NA	47% morbidity and 5% mortality but calculated in the mixed cohort of patients with recurrent and primary disease.

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the same approach throughout their cohort, with the exception of Spiliotis et al[78] and Bakrin et al,[76] who used both the open and closed techniques at a ratio of 2:1. An analysis, however, of the influence of either technique on the survival outcomes was not provided in either study.

Survival Rates

Overall Survival

The primary end point in all studies was either mean/median overall survival (in months) or the 5-year survival rate. In the randomized controlled trial by Spiliotis et al,[78] the mean survival in the HIPEC group (26.7 months) was significantly longer than the mean survival of patients who did not receive HIPEC (13.4 months; $P = 0.006$). Furthermore, in platinum-sensitive cases, a statistically significant difference was observed between the HIPEC and non-HIPEC groups, with mean overall survivals of 26.8 and 15.2 months, respectively ($P = 0.035$). A nonstatistically significant benefit was also observed in the platinum-resistant cases treated with HIPEC.

Similarly, Fagotti et al[72] reported a 5-year overall survival of 68.4% in the HIPEC group compared with 42.7% in the non-HIPEC group ($P = 0.017$). Both treatment groups received optimal CRS and systemic chemotherapy with oxaliplatin. Furthermore, in a smaller Level III study, Muñoz-Casares et al[83] reported a global 5-year overall survival of 57% in the HIPEC group compared with 17% in the non-HIPEC group ($P = 0.046$), rising to 67% and 29% in the HIPEC and non-HIPEC groups, respectively, in patients who had undergone optimal cytoreduction without macroscopically residual tumor (CC 0 score). In addition, Safra et al[79] reported a 5-year overall survival of 79% in the group receiving CRS and HIPEC compared with 45% in the group receiving only systemic chemotherapy ($P = 0.016$). It is of further note that Ceelen et al,[73] Deraco et al,[80] and Roviello et al[81] reported 5-year overall survival rates of 41.3%, 23%, and 44%, respectively, in patients receiving both CRS and HIPEC.

Six studies reported median overall survival: Ceelen et al[73] (37 months), Cotte et al[74] (28.4 months), Deraco et al[80] (25.7 months), and Delotte et al[77] (35 months). Königsrainer et al[53] reported a median survival of 35 months in patients with optimum cytoreduction (CC score = 0/1) and only 14 months in those with a CC score of 2/3. In the largest study by Bakrin et al,[76] the median survival was 45.7 months and the survival rate decreased from 89% at year 1 to 37% at year 5. Finally, Piso et al[75] reported a mean survival of 30 ± 6 months.

Three studies presented ill-defined end points; however, their findings are still of relevance. Zivanovic et al[54] reported that, after a median follow-up of 20.6 months (range, 13.9–27.6 months), there was an overall survival rate of 66.6%. Similarly, during a median follow-up of 16 months (range, 5–23 months), Argenta et al[55] reported an overall survival rate of 90%. Finally, Gouy et al[56] reported an overall survival rate of 100% during a median follow-up of 32 months (range, 25–56 months).

Disease-Free Survival

Eleven studies reported DFS. Ceelen et al[73] and Deraco et al[80] reported a 5-year DFS rate of 12.5% and 7%, respectively. Cascales-Campos et al[82] reported a 3-year DFS rate of 45% in the HIPEC group compared with 23% in the non-HIPEC cohort. Muñoz-Casares et al[83] reported a mean DFS of 48 ± 42 months in the HIPEC group compared with 24 ± 18 months in the non-HIPEC cohort. Safra et al[79] reported a median DFS of 15 months in the HIPEC group compared with 6 months in the non-HIPEC cohort. Furthermore, median DFSs were also reported by Zivanovic et al[54] (13.6 months), Cotte et al[74] (8.5 months), and Delotte et al[77] (15.6 months). It is also of note that, after a median follow-up of 16 months (range, 5–23 months) and 32 months (range, 25-56 months), Argenta et al[55] and Gouy et al,[56] respectively, reported DFS rates of 70% and 28.6%.

Finally, Fagotti et al[72] reported that, during a median follow-up period of 45 months in the HIPEC group and 36 months in the non-HIPEC cohort, 0% of patients in the non-HIPEC group were disease-free, whereas 33.3% of the HIPEC cohort remained disease-free. It is also of interest that Fagotti et al[72] reported a statistically significant ($P = 0.004$) longer median time between treatment and recurrence in the HIPEC group (26 months; range, 5–73 months) compared with the non-HIPEC cohort (15 months; range, 4–58 months). Furthermore, a nonstatistically significant ($P = 0.07$) prolongation of the time between treatment and recurrence relative to initial recurrence from primary disease was noted in 53.4% of the HIPEC group and 32.4% of the non-HIPEC cohort.[72]

Morbidity

Most studies assessed morbidity associated with a CRS and HIPEC. Six studies[55,76,77,80–82] ranked morbidity using the Common Terminology Criteria for Adverse Events classification[85] (grades I-V). Using these criteria, Deraco et al[80] reported that 26.3% of patients experienced grade III to V adverse events. The most frequent events were bone marrow depression (n = 7), gastrointestinal fistulation (n = 5), anemia (n = 5), and renal failure (n = 3). Other adverse events included pleural effusion, postoperative bleeding, abdominal abscess, urinary tract infection, and leukopenia. In addition, the procedure-related mortality rate was 5.3% (n = 3) caused by an anastomotic leak, severe pneumonia, and sepsis. Argenta et al[55] reported a grade III to IV morbidity of 30%, with the adverse events reported being 1 instance of grade III acute renal injury and 2 instances of grade IV thrombocytopenia and neutropenia. In comparison, Delotte et al[77] reported 20% of patients experiencing grade III to IV complications, whereas Roviello et al,[81] with a smaller cohort, reported only 12% of patients experiencing grade III to IV complications. Bakrin et al[76] reported grade III to IV complications in 30% of procedures performed for advanced or recurrent disease without further subgroup analysis. Finally, Cascales-Campos et al[82] reported an overall morbidity rate of 23% in the non-HIPEC group (14% rated grades III–IV) compared with 28% in the HIPEC group (21% rated grades III–IV).

Three studies[53,56,83] ranked morbidity using the Clavien-Dindo Scale.[69] Königsrainer et al[53] reported a 42% overall morbidity (grades I-IV). No significant difference was noted when patients were compared for the completeness of cytoreduction (CC 0/1 compared with CC 2/3). Gouy et al[56] reported that all patients experienced early grade II to III

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morbidity, with 6 patients (86%) experiencing extra-abdominal grade II complications—namely, an infected central catheter, UTI, transient hematological toxicity, and transient confusional syndrome. One instance of a grade III lymphocyst was reported that required drainage twice. In addition, Muñoz-Casares et al[83] reported mainly grade I to II morbidity, with similar rates in the HIPEC (29%) and non-HIPEC (25%) groups.

Ceelen et al[73] reported major morbidity of 21% (n = 9 of 42), including 3 patients who required reoperation for ureteric necrosis, staple line bleeding, and thoracic empyema. They also reported minor morbidity of 43% (n = 18 of 42), with the most frequent events being prolonged ileus, UTI, and wound infection. Cotte et al[74] reported major morbidity in 13.6% of patients, where anastomotic leakage (n = 3), pleural effusion requiring drainage (n = 3), and grade 3 leukopenia (n = 2) were the most common complications observed. Zivanovic et al[54] reported severe adverse events occurring in 25% of patients, including a grade III postoperative intra-abdominal collection and pancreatic leak, a grade III unilateral ureteric injury, and sepsis. Finally, Safra et al[79] reported that all patients experienced mild electrolyte abnormalities, with mild nausea being a common symptom. No major bleeding events or perioperative mortality was observed.

DISCUSSION

To our knowledge, this is the most recent systematic review to examine the impact of HIPEC on patients with recurrent ovarian cancer undergoing maximum CRS. The included studies demonstrate that HIPEC is associated with improved median survival time and 5-year survival rate with acceptable morbidity and no added mortality. In particular, a randomized controlled study demonstrated that the overall survival is doubled in patients receiving HIPEC (26.7 vs 13.4 months).[78] This is in accordance with the results of most Level IV studies included in this review, reporting overall survival in excess of 24 months and as high as 46 months in the largest multicenter study.[76] In addition, 3 Level III studies reported 5-year survival rates in excess of 50%, which was significantly higher than the survival rate in patients who were only treated with optimum CRS. Median survival was found to be broadly similar, within a general range of 25.7 to 45.7 months, dropping to 14 months in patients where complete cytoreduction (CC-0) was not achieved.

Disease-free survival was not assessed by all investigators, but the aforementioned Level 3 studies[72,83] reported a benefit for HIPEC patients, with 33% of this group disease-free after almost 4 years in the study by Fagotti et al.[72] Most studies assessed morbidity using either the Common Terminology Criteria for Adverse Events (CTCAEv3)[85] or the Clavien-Dindo classification[69] and reported rates between 20% and 40%; only 1 study[83] allowed direct comparison of morbidity between HIPEC and non-HIPEC patients, with no demonstrable difference between the treatment arms.

The typical survival benefit afforded by varying levels of CRS in the absence of HIPEC can be derived from a number of Level 1,[70,71] Level 2,[57] and Level 4[58,59] publications assessed by this review. Cohort studies such as DESKTOP OVAR[58] (N = 267) reported a median survival of 45.2 months for patients who had complete cytoreduction compared with 19.7 months for those with residual macroscopic tumor. Similarly, the CALYPSO trial[57] (N = 975) reported a statistically significant ($P < 0.001$) survival of 45.2 months in patients undergoing complete cytoreduction compared with 29.7 months in those with residual disease. These figures are broadly similar to those reported for patients treated with HIPEC and cytoreduction; however, there are significant limitations that prevent a direct comparison between these studies and those reporting HIPEC outcome measures. In particular, the majority of the studies referenced both in this review and in reviews of CRS efficacy are retrospective, leading to inevitable selection bias.

Heated IntraPEritoneal Chemotherapy offers multiple advantages by virtue of both its hyperthermic environment and intraperitoneal administration that may explain the improved survival data. The slow rate of clearance from the peritoneal cavity into the plasma allows the use of higher chemotherapy doses, delivered via the intraperitoneal route, when compared with systemic chemotherapy. Depending on the drug used, the intraperitoneal-to-plasma AUC (area under concentration-time curve) ratio may be greater than 1000.[60] This therefore allows preferential targeting of the tumor area while reducing the risk of systemic complications.

Furthermore, the hyperthermic environment has an effect both on tumor cells and on the efficacy of cytotoxic drugs. A breadth of evidence indicates that malignant cells are selectively destroyed when exposed to temperatures of 41°C to 43°C.[61–63] An increase in lysosomal activity is known to selectively occur in malignant cells. In addition, a decrease in blood flow in the microcirculation of malignant tissue has been observed.[64] This, alongside a decrease in oxidative metabolism, increases intracellular lactic acid levels, lowering the pH and further increasing lysosomal activity.[62] Finally, a synergistic effect between hyperthermia and cytotoxic drugs has been proposed. This is thought to be caused by several mechanisms. Uptake of the drug into malignant cells is greater because of increased membrane permeability and transport activity.[70] Tissue penetration depth is believed to be increased.[63,65] Evidence exists that suggests that hyperthermia may affect the drug pharmacodynamics and excretion pathways, leading to higher intracellular concentrations.[66] This enhancing effect is known to occur in differing degrees, depending on the agent used.

The majority of studies included in this review were mostly Level IV. They are characterized by heterogeneous cohorts that were treated at different time points and received different chemotherapy regimens for their primary disease. In addition, there is not an internationally accepted protocol for HIPEC administration. Across the studies reviewed, patients received different chemotherapy drugs at different temperatures and for widely variable durations of time. Given that the pharmacokinetic benefits of HIPEC are affected by choice of agent and level of hyperthermia, it may be hypothesized that these variations could have a significant effect on patient outcomes.

At the time of writing, 2 randomized control trials—the French study CHIPOR (NCT01376752) and the Italian study HORSE (NCT01539785)—are currently recruiting patients. Both studies, estimated to be completed in the second half of

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2018, investigate the addition of HIPEC to maximal CRS using cisplatin 75 mg/m^2, where each patient has been pretreated with neoadjuvant chemotherapy. Primary outcome of interest in CHIPOR is overall survival, with relapse-free survival a secondary outcome. In comparison, HORSE uses progression-free interval as its primary outcome, with overall survival as a secondary outcome. Follow-up times in CHIPOR and HORSE are 4 years and 3 years, respectively, with respective estimated enrollment figures of 444 and 158 patients. These will potentially provide definitive evidence regarding the true nature of the survival benefit afforded by HIPEC in patients with recurrent ovarian cancers and may even allow identification of optimum treatment protocols and subgroups of patients who are most likely to benefit from this approach.

CONCLUSIONS

Heated IntraPEritoneal Chemotherapy seems to be associated with improved overall survival and DFS in patients with recurrent ovarian cancer. Heated IntraPEritoneal Chemotherapy should be considered for all such patients despite the limitations of the studies included in this review. Large, international, prospective studies are required to further quantify the true efficacy of HIPEC and to identify the optimal drug regimen and intraoperative conditions to achieve a maximal survival benefit.

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