Heated IntraPEritoneal Chemotherapy (HIPEC) for patients with recurrent ovarian cancer: A systematic literature review.

Short title: Recurrent ovarian cancer and HIPEC

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ABSTRACT

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

Method: 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 while secondary outcomes included disease-free survival and HIPEC-related morbidity.

Results: Sixteen studies with 1,168 patients were analysed. Most studies were Level 4, with four studies graded as Level 3 and one Level 2. 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 – 35 months, with disease-free survival varying between 8.5 – 48 months. HIPEC appears to confer survival benefits to patients with recurrent disease with a randomised 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). HIPEC-related morbidity ranged between 13.6 – 100 % but it was mainly minor and not significantly different to that experienced by patients who only underwent cytoreduction.

Conclusion: Cytoreductive surgery and HIPEC appear 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 maximum survival benefit.

INTRODUCTION

Ovarian cancer accounts for more deaths than any other gynaecological 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 USA, more than 15,000 women die every year from the disease. Recent population-based studies have indicated a five-year age-standardised relative survival of 31% in the UK, compared with a European rate of 37%[4]. The low survival rate is due to the non-specific 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 over four years but no change has been achieved in overall survival during the last three decades[6]. Although 70-80% of patients respond to the initial therapy, typically only 15% are cured with the remaining developing drug-resistant recurrent disease[7,8,9,10]. The median survival of patients with recurrent ovarian cancer ranges between 12-24 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 1[11,12,13] and Level 3[14,15,16] evidence demonstrating its benefits in patients with other abdominal malignancies (e.g. advanced colon or gastric cancer). Furthermore, bidirectional

chemotherapy using intravenous paclitaxel or ifosfomide and intraperitoneal cisplatin and paclitaxel appears 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 while secondary outcomes were defined as disease-free survival 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 cytoreductive surgery (CRS) with HIPEC for recurrent ovarian cancer. A clinical trials database (www.clinicaltrials.gov) was also searched for randomised controlled trials. The search strategy included the text terms “recurrent ovarian cancer”, “cytoreductive surgery/cytoreduction”, “hyperthermic/heated intraperitoneal chemotherapy” and “HIPEC”. The keywords 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 manuscript was determined as being irrelevant (e.g. primary ovarian cancer, mixed cohort with primary and recurrent disease not performing subgroup analysis, study not assessing 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. Two reviewers (AH and DD) 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, sixteen studies were identified that were eligible for analysis (*Figure 1*). They included 1,168 patients with recurrent ovarian cancer who underwent CRS, of which 81.6% (n=953) received HIPEC. Eleven studies were Level IV, with four graded as Level III and one as Level II (*Table 1*). On initial assessment, wide variations were observed in the choice of HIPEC drug-regime and technique (i.e. temperature of perfusate, duration and open or closed technique).

Choice of HIPEC drugs/regimen

Fourteen studies included one platinum-based agent (either cisplatin, oxaliplatin or carboplatin). Eight studies[19-26] used these drugs in isolation. Piso *et al*[26] used either cisplatin or mitoxantrone but did not elaborate further as to how many patients received each drug. In the largest multicentre study[27] 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[28-32] used cisplatin with doxorubicin[28,30,31], paclitaxel[29] or mitomycin[30-32]. Three studies used oxaliplatin[22-24], with only one study electing to use it in combination (with irinotecan in some patients). Spiliotis *et al*[29] used a combination of doxorubicin, paclitaxel and mitomycin to treat a subgroup of patients who were platinum resistant. Finally, two studies[33-34] reported the use of paclitaxel at a dose of 60 mg/m^2 for 60 mins at 41-43 ^oC[26].

Cisplatin group

Eleven studies used cisplatin with doses ranging from 20 mg/m^2 to 250 mg/m^2. Bakrin *et al*[27] used 50 mg/m^2 and most studies used a dose between 50-100 mg/m^2. Only Ceelen *et al*[24] used a higher dose (100-250 mg/m^2) whereas the lowest dose (20 mg/m^2) was used by Cotte *et al*[25]. Infusion time was varied between sixty minutes[28,29,32] and one hundred and twenty minutes[24-27,30,31]; additionally, the target temperatures of the perfusate varied between 40.5^{o}C[24] to as high as 46^{o}C[25].

Oxaliplatin group

Three studies used oxaliplatin to treat fifty-four patients[22-24]. Two studies used this in isolation; a dose of 460 mg/m^2 was used with an infusion time of thirty minutes. The target temperatures of the perfusate were close to 40.5^{o}C[24] and 41.5^{o}C[23]. The third study[22] used oxaliplatin (460 mg/m^2) or oxaliplatin (360 mg/m^2) and irinotecan (360 mg/m^2) with an infusion time of thirty minutes at 43^{o}C.

Carboplatin group

Two studies used carboplatin.[21,30] One study used it in isolation to treat ten patients at a dose of 1000 mg/m^2 for ninety minutes at 40-43^{o}C[21]. The second study used carboplatin with paclitaxel 60 mg/m^2 for one hundred and twenty minutes at 42.5^{o}C to treat an undisclosed number of patients[30].

Paclitaxel group

Two studies used paclitaxel at 60 mg/m^{2}as the sole HIPEC agent[33,34]. The temperature of the perfusate was similar in both studies ranging between 41-43^{o}C. However, one study used an infusion time of sixty minutes[34], while in the second no infusion time is reported[33]. Additionally, paclitaxel was used in two other studies, in combination with cisplatin[29] and carboplatin[30].

Platinum-resistant group

Only one study[29] 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 to cisplatin 100 mg/m^2 and paclitaxel 175 mg/m^2 for platinum sensitive cases (n = 34). Additionally, Deraco *et al*[31] made reference to two patients who were treated with doxorubicin for platinum-resistant disease.

Open versus Closed Technique

HIPEC 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 minimised, allowing better maintenance of the hyperthermic state[35].

Five hundred and eighty (60.9%) HIPEC procedures were performed using the open method, while three hundred and twenty-four (39.1%) were carried out using the closed technique. All studies used the same approach throughout their cohort, with the exception of Spiliotis[29] and Bakrin[27], 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 (months) or the 5-year survival rate. In the randomised controlled trial by Spiliotis[29], the mean survival in the HIPEC group (26.7 months) was significantly better 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 months and 15.2 months respectively (p=0.035). A non-statistically significant benefit was also observed in the platinum-resistant cases treated with HIPEC.

Similarly, Fagotti *et al*[23] reported a five-year overall survival of 68.4% in the HIPEC group, compared to 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 3 study, Munoz-Casarez *et al*[34] reported a global five-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 tumour (CC 0 score). Additionally, Safra *et al*[30] reported a five-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[24], Deraco[31] and Roviello[32] reported five-year overall survivals of 41.3%, 23% and 44 respectively in patients receiving both CRS and HIPEC.

Six studies reported median overall survival (months): Ceelen[24] (37 months), Cotte[25] (28.4 months), Deraco[31] (25.7 months) and Delotte[28] (35 months). Königsrainer[19] 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*[27], 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*[26] reported a mean survival of 30 ± 6 months.

Three studies presented ill-defined endpoints; however, their findings are still of relevance. Zivanovic *et al*[20] reported that, after a median follow up of 20.6 months (range: 13.9-27.6), there was an overall survival of 66.6%. Similarly, over a median follow up of 16 months (range: 5-23), Argenta *et al*[21] reported an overall survival of 90%. Finally, Gouy *et al*[22] reported an overall survival of 100% over a median follow up of 32 months (range: 25-56).

Disease Free Survival

Eleven studies reported disease free survival (DFS). Ceelen[24] and Deraco[31] reported a five-year DFS of 12.5% and 7% respectively. Cascales-Campos *et al* reported a three-year DFS of 45% in the HIPEC group, compared with 23% in the non-HIPEC cohort. Munoz-Casares *et al*[34] reported a mean disease-free survival of 48 ± 42 months in the HIPEC group, compared with 24 ± 18 months in the non-HIPEC cohort. Safra *et al* reported a median disease-free survival of 15 months in the HIPEC group compared with 6 months in the non-HIPEC cohort. Furthermore, median disease-free survivals were also reported by Zivanovic[20] (13.6 months), Cotte[25] (8.5 months) and Delotte[28] (15.6 months). It is also of note, that after a median follow up of 16 months (range: 5-23) and 32 months (range: 25-56), Argenta[21] and Gouy[22] respectively reported disease-free survivals of 70% and 28.6%.

Finally, Fagotti *et al*[23] reported that, over 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, while 33.3% of the HIPEC cohort remained disease free. It is also of interest that Fagotti 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 to the non-HIPEC cohort (15 months, range 4-58 months). Furthermore, a non-statistically 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[23].

Morbidity

Most studies assessed morbidity associated with a CRS and HIPEC. Six studies[21,27,28,31-33] ranked morbidity using the Common Terminology Criteria for Adverse Events (CTCAE) classification[36] (Grade I-V). Using these criteria, Deraco *et al*[31] reported that 26.3% of patients experienced Grade III-V adverse events. The most frequent events were bone marrow depression (n=7), gastrointestinal fistulation (n=5), anaemia (n=5) and renal failure (n=3). Other adverse events included pleural effusion, post-operative bleeding, abdominal abscess, UTI and leucopenia. Additionally, the procedure-related mortality was 5.3% (n=3), due to an anastomotic leak, severe pneumonia and sepsis. Argenta *et al*[21] reported a Grade III-IV morbidity of 30%, with the adverse events reported being one instance of Grade III acute renal injury and two instances of Grade IV thrombocytopenia and neutropenia. In comparison, Delotte *et al*[28] reported 20% of patients experiencing Grade III-IV complications, while Roviello *et al*[32], with a smaller cohort, reported only 12% of patients experiencing Grade III-IV complications. Bakrin *et al*[27] reported grade III-IV complications in 30% of procedures performed for advanced or recurrent disease without further subgroup analysis. Finally, Cascales-Campos *et al*[33] reported overall morbidity of 23% in the non-HIPEC group (14% rated Grade III-IV) compared with 28% in the HIPEC group (21% rated Grade III-IV).

Three studies[19,22,34] ranked morbidity using the Clavien-Dindo scale[37]. Konigsrainer *et al*[19] reported a 42% overall morbidity (Grade 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* reported that all patients experienced early Grade II-III morbidity, with six patients

(86%) experiencing extra-abdominal Grade II complications – namely an infected central catheter, UTI, transient haematological toxicity and transient confusional syndrome. One instance of a Grade III lymphocyst was reported which required drainage twice. Additionally, Munoz-Casares *et al*[34] reported mainly Grade I-II morbidity, with similar rates in the HIPEC (29%) and non-HIPEC (25%) groups.

Ceelen[24] reported major morbidity of 21% (n=9/42) including three patients that required reoperation – for ureteric necrosis, staple line bleeding and thoracic empyema. They also reported minor morbidity of 43% (n=18/42), with the most frequent events being prolonged ileus, UTI and wound infection. Cotte[25] 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[20] reported severe adverse events occurring in 25% of patients, including a Grade 3 postoperative intra-abdominal collection and pancreatic leak, a Grade 3 unilateral ureteric injury and sepsis. Finally, Safra [30] 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 for patients with recurrent ovarian cancer undergoing maximum cytoreductive surgery. The included studies demonstrate that HIPEC improves the median survival time and 5-year survival rate with acceptable morbidity and no added mortality. In particular, a randomised controlled study demonstrated that the overall survival is doubled in patients receiving HIPEC (26.7 months vs 13.4 months).[29] This is in accordance with the results of most Level 4 studies included in this review, reporting overall survival in excess of 24 months and as high as 46 months in the largest multicentre study[27]. In addition, three Level 3 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 cytoreductive surgery. 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[23,34] reported a benefit for HIPEC patients with 33% of this group disease free after almost 4 years in the study by Fagotti *et al*[23]. Most studies assessed morbidity using either the Common Terminology Criteria for Adverse Events (CTCAEv3)[36] or the Clavien-Dindo classification[37], and reported rates between 20% and 40%; only one study[34] 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 cytoreductive surgery in the absence of HIPEC can be derived from a number of Level 1[38,39], Level 2[40] and Level 4[41,42] publications assessed by this review. Cohort studies such as DESKTOP OVAR[41] (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 tumour, respectively. Similarly, the CALYPSO trial[40] (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 which 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.

HIPEC offers multiple advantages by virtue of both its hyperthermic environment and intraperitoneal administration which 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 to systemic chemotherapy. Depending on the drug used, the intraperitoneal-to-plasma AUC (area under concentration-time curve) ratio may be greater than 1000[43]. This therefore allows preferential targeting of the tumour area while reducing the risk of systemic complications.

Furthermore, the hyperthermic environment has an effect both on tumour cells and on the efficacy of cytotoxic drugs. A breadth of evidence indicates that malignant cells are selectively

destroyed when exposed to temperatures of 41-43^{o}C[44-46]. An increase in lysosomal activity is known to selectively occur in malignant cells. Additionally, a decrease in blood flow in the microcirculation of malignant tissue has been observed[47]. This, alongside a decrease in oxidative metabolism, increases intracellular lactic acid levels, lowering the pH and further increasing lysosomal activity[45]. Finally, a synergistic effect between hyperthermia and cytotoxic drugs has been proposed. This is thought to be due to several mechanisms. Uptake of the drug into malignant cells is greater due to increased membrane permeability and transport activity[38]. Tissue penetration depth is believed to be increased[46,48]. Evidence exists which suggests that hyperthermia may affect the drug pharmacodynamics and excretion pathways, leading to higher intracellular concentrations[49]. 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 4. They are characterised by heterogeneous cohorts that were treated at different time points and received different chemotherapy regimens for their primary disease. Additionally, 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 hypothesised that these variations could have significant effect on patient outcomes. At the time of writing, two randomised control trials – the French study CHIPOR (NCT01376752) and the Italian study HORSE (NCT01539785) – are recruiting patients. These will 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.

CONCLUSION

The administration of HIPEC appears to improve both overall survival and disease-free survival in patients with recurrent ovarian cancer. HIPEC 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 regime and intraoperative conditions in order to achieve maximal survival benefit.

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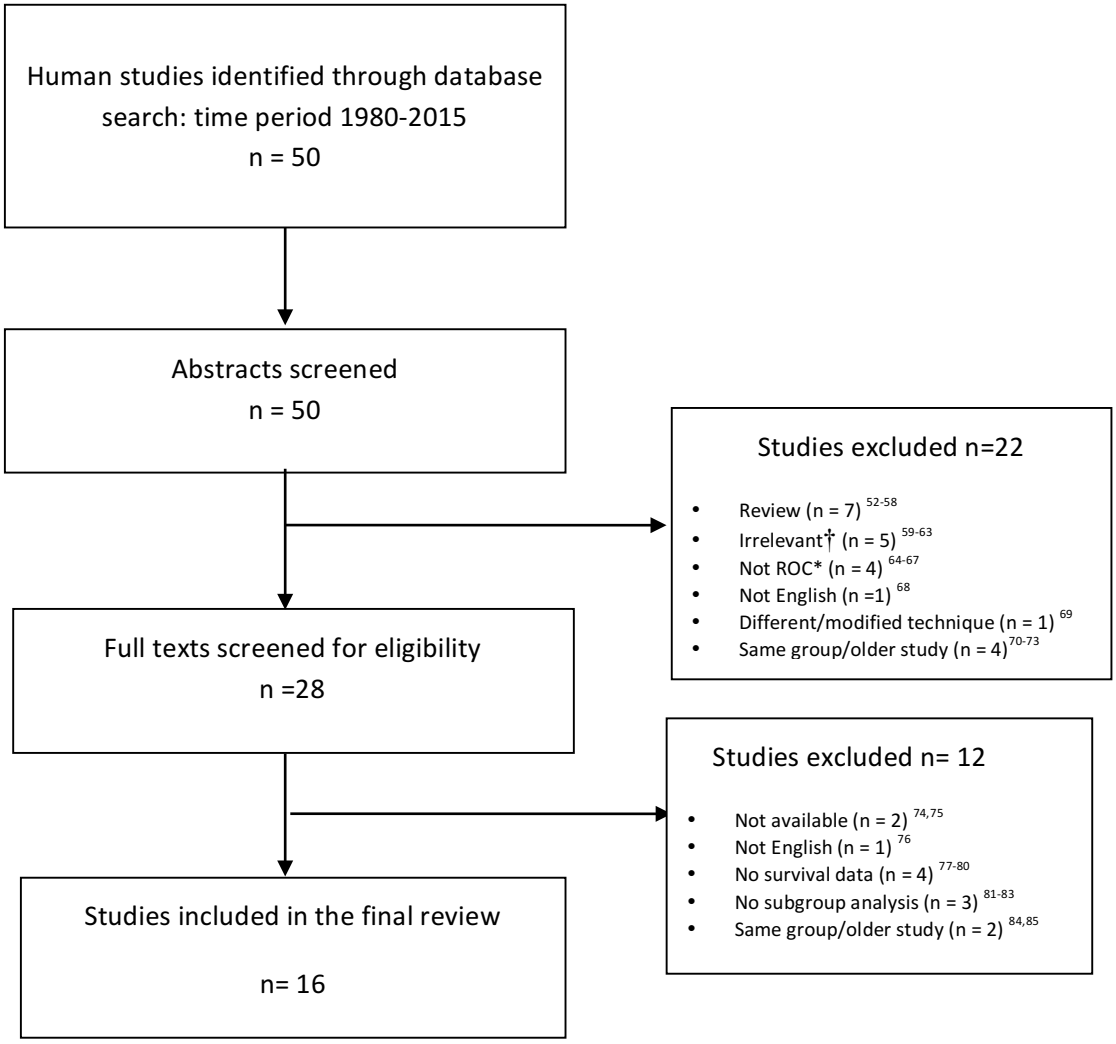
Figure 1. – Diagrammatic illustration of the search strategy



*ROC=Recurrent ovarian cancer

† No survival data, no subgroup analysis

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

Abbreviations: RCT: Randomised Control Trial; CRS: cytoreductive surgery; HIPEC: Heated Intraperitoneal Chemotherapy; OS: Overall Survival; DFS: Disease-Free Survival

Author	Year	Number	Age (years)	Design (Level of Evidence)	HIPEC Drugs	Peritoneal carcinomatosis index (PCI)	Completeness of cytoreduction(CC)	Technique (Open or closed)	Overall survival (OS)	Disease free survival (DFS)	Morbidity
Delotte	2015	15	72(70-77)	Single centre retrospective Level 4 CRS+HIPEC	Cisplatin (50 mg/m^2) and doxorubicin(15 mg/m^2) for 60 mins at 43.0ºC	11(3-22)	CC-0=60% CC-1=40%	Open	Median OS: 35(28-not reached) months	15.6 months (median)	20% grade III or IV complications
Cascales-Campos	2015	Total: 54 HIPEC: 32 Non-HIPEC: 22	HIPEC: 54 (40-78) Non-HIPEC: 55 (37-73)	Case control Level 3 CRS + HIPEC + chemo CRS + chemo	Paclitaxel 60 mg/m^2 at 42ºC	HIPEC: 8 (2-23) Non-HIPEC: 4 (2-16)	CC-0=54	Open	N/A	At 3 years: HIPEC: 45% Non-HIPEC: 23%	HIPEC: 28% (21% Grade III/IV) Non-HIPEC: 23% (14% Grade III/IV)
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 100mg/m^2 + paclitaxel 175mg/m^2 for 60 mins at 42.5ºC Platinum resistant: doxorubicin 35mg/m^2 + paclitaxel 175mg/m^2 or mitomycin 15mg/m2 for 60 mins at 42.5ºC	HIPEC:48% ≥10 NonHIPEC:50% ≥10	HIPEC: CC-0 65% NonHIPEC: CC-0 55%	Open: 40 Closed: 20	HIPEC mean OS: 26.7 months Non-HIPEC mean OS: 13.4 months Platinum sensitive HIPEC mean OS: 26.8 months Platinum sensitive non-HIPEC mean OS: 15.2 months	N/A	N/A
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 60mg/m^2 + carboplatin (AUC-4) or cisplatin 25mg/l/m^2 + mitomycin-C 3.3 mg/l/m^2 for 120 mins at 42.5ºC	N/A	N/A	Closed	At 5 years HIPEC: 79% Non-HIPEC: 43%	HIPEC: 15 months (median) Non-HIPEC: 6 months (median)	All patients experienced mild electrolyte abnormalities
Konigsrainer	2014	90	55 (18-76)	Single centre, retrospective, Level 4	Cisplatin 50 mg/m^2 for 90 mins at 42.0ºC	20(3-39)	CC-0=52% CC-1=17% CC-2=6% CC-3=25%	Open	Median OS CC-0/1= 35 (95% CI 23-46) months Median OS CC-2/3= OS 14 (95%CI 4-25)	NA	42% overall complication rate (Grade I –IV)
Zivanovic	2014	12	54 (40-70)	Single centre, prospective cohort Level 4	Cisplatin at either 60 mg/m^2 (n=3), 80 mg/m^2 (n=33) or 100 mg/m^2 (n=6) for 90 mins at 41-43ºC	15.5 (4-28)	CC-0: 58% CC-1: 8% CC-2: 34%	Closed	At median follow up of 20.6 months (13.9-27.6), OS = 66.6%	13.6 months (median)	25% (SEVERE)
Bakrin	2013	474	57.4 (22.6-77.6)	Multicentre,Retrospective, Level 4	Cisplatin was the most commonly used drug(75%) at a dose of 50 (30-100) mg/m^2 for 90 (30-120)mins at 42 (15-45) ºC	0-8 (52%) >8 (48%)	CC-0=75% CC-1,2,3=25%	Open:329 Closed:145	Median OS=45.7 months 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
Argenta	2013	10	56 (47-66)	Prospective cohort Level 4	Carboplatin 1000 mg/m^2 for 90 mins at 40-43ºC	N/A	CC-0: 6 CC-1: 4	Closed	At median follow up of 16 months (5-23), OS = 90%	At median follow up of 16 months (5-23): 70%	30% Grade III/IV
Gouy	2013	7	53 (27-61)	Retrospective cohort Level 4	Oxaliplatin 460mg/m^2 or Oxaliplatin 360 mg/m^2 + Irinotecan 360 mg/m^2 for 30 mins at 43ºC	N/A	CC-0: 7	Open	At median follow up of 32 months (25-56), OS = 100%	At median follow up of 32 months (25-56): 28.6%	All patients experienced early Grade II/III 14% Grade III
Fagotti	2012	Total: 67 HIPEC: 30 Non-HIPEC: 37	HIPEC: 51 (41-63) Non-HIPEC: 55 (32-69)	Case control Level 3 CRS + HIPEC CRS + chemo	Oxaliplatin 460 mg/m^2 for 30 mins at 41.5ºC	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-year OS: 68.4% Non-HIPEC 5-year OS: 42.7%	HIPEC (45 months median follow up): 33.3% Non-HIPEC (36 months median follow up: 0%	N/A
Deraco	2012	56	55.2 (30-75)	Cohort Level 4 CRS+ HIPEC + chemo	Cisplatin (42 mg/L) + doxorubicin (15mg/L) in 4-6L perfusate or cisplatin (25 mg/L/m^2) + mitomycin-C (3.3 mg/L/m^2) for 90 mins at 42.5ºC	15.2 (4-30) (median)	CC-0 = 47 CC-1 = 7 CC-2 = 1 Unknown = 1	Closed	5-year OS: 23% Median OS: 25.7 months	At 5 years: 7%	26.3% (SEVERE) 5.3% procedure related mortality
Ceelen	2012	42	54 (22-71)	Cohort Level 4 Pretreated + CRS + HIPEC + chemo	Cisplatin (100-250 mg/m^2) for 90 mins or Oxaliplatin (460 mg/m^2) for 30 mins at 40.5-41ºC	4 (2-7) (median)	CC-0 = 50% CC-1 = 36% CC-2 = 14%	Open	5-year OS: 41.3% Median OS: 37 months	At 5 years: 12.5%	21% MAJOR
Roviello	2010	8	56(28-72)	Single centre cohort Level 4 CRS+HIPEC	Cisplatin (100mg/mq) and mitomycin C (25mg/mq) for 60mins at 41-43 ºC	PCI 1-6 (87.5%) PCI>15 (12.5%)	CC-0=75% CC-1=25%	Closed	5-year survival probability=44±22%	N/A	Grade III/IV complications in 12%
Munoz-Casares	2009	Total=26 HIPEC=14 Non-HIPEC=12	HIPEC:54(28-68) NonHIPEC:54(30-67)	Single centre, non-randomised case-controlled Level 3 CRS + HIPEC + Chemo CRS + chemo	Paclitaxel(60 mg/m^2) for 60mins at 41-43 ºC	HIPEC=13±6 NonHIPEC=13±6	CC-0 HIPEC =64% NonHIPEC=58%	Open	5-year OS HIPEC=57% NonHIPEC=17%	HIPEC=48±42months NonHIPEC=24±18months	HIPEC=29% NonHIPEC=25% Mainly grade I and II
Cotte	2007	65	54.3 (30-75)	Cohort Level 4 CRS + HIPEC + chemo	Cisplatinum 20mg/m^2 for 90 minutes at 44-46ºC	N/A	N/A	Closed	Median OS: 28.4 months	8.5 months (median)	13.6% MAJOR
Piso	2004	11	54(36-79)	Single centre cohort Level 4 CRS + HIPEC ± chemo	Mainly cisplatin at a dose of 75 mg/m^2 for 90 mins at 41.5 ºC	NA	N/A	Open	Mean OS=30±6 months	NA	47% morbidity and 5% mortality but calculated in the mixed cohort of patients with recurrent and primary disease.