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Corresponding author: Stefano Cianci

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Original Article

Hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer recurrence: systematic review and meta-analysis

Stefano Cianci[1], Gaetano Riemma[1], Carlo Ronsini[2], Pasquale De Franciscis[1], Marco Torella[1], Antonio Schiattarella[1], Marco La Verde[1], Nicola Colacurci[1]

[1]Department of Woman, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Naples, Italy; [2]Gynecologic and Obstetrics Unit, Università "G. d'Annunzio", Chieti, Italy

Contributions: (I) Conception and design: All authors; (II) Administrative support: S Cianci, G Riemma; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: S Cianci, G Riemma, C Ronsini; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Stefano Cianci, MD, PhD. Department of Woman, Child and General and Specialized Surgery, University of Campania "Luigi Vanvitelli", Largo Madonna delle Grazie, 1 80138 Naples, Italy. Email: stefano.cianci@unicampania.it.

Background: Ovarian cancer is the first cause of death among gynecological malignancies with a high incidence of recurrence. Different treatment options are suitable to prolong the survival rate of these patients. Over the last years, one of the most intriguing methods, adopted in different oncologic centers worldwide, is the hyperthermic intraperitoneal chemotherapy (HIPEC).

Methods: A meta-analysis was performed to value the role of HIPEC for ovarian cancer recurrence. Search strategy was conducted with a combination of the following keywords: "ovarian recurrence, ovarian cancer recurrence, peritoneal cancer recurrence, ovarian recurrence AND HIPEC, secondary cytoreduction HIPEC". Seven studies were selected for analysis.

Results: In women with recurrent ovarian cancer (ROC), the use of HIPEC in addition to cytoreductive surgery and chemotherapy significantly improved 1-year overall survival (OS) when compared to protocols without HIPEC (OR 2.42; 95% CI, 1.06–5.56; P=0.04; I^2=4%). The improvement in OS was maintained significant also after 2, 3 and 5 years respectively (OR 3.33; 95% CI, 1.81–6.10; P<0.01; I^2=0%), (OR 4.22; 95% CI, 2.07–8.60; P<0.01; I^2=54%), (OR 5.17; 95% CI, 1.40–19.09; P=0.01; I^2=82%).

Conclusions: HIPEC seems to have an effective role to prolong survival in patients affected by ROC.

Keywords: Ovarian cancer; hyperthermic intraperitoneal chemotherapy (HIPEC); loco-regional treatment; peritoneal carcinosis; recurrence; chemotherapy

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Introduction

Ovarian cancer is the first cause of death among gynecologic malignancies (1). The surgical treatment represents the first option with the aim to achieve the optimal debulking, followed by systemic chemotherapy (2). However, even achieving complete cytoreduction the majority of patients at stage III-IV develops a recurrence in a few years (3). To date, different treatment options are suitable to prolong the survival rate of these patients as monoclonal antibodies and targeted therapies as bevacizumab or PARP inhibitors, and biological therapy. However, the results obtained are still partial and not completely effective (4). One of the most attractive methods, currently available in several oncologic centers, is the hyperthermic intraperitoneal chemotherapy (HIPEC). It is an effective method to deliver antiblastic drugs directly in the abdomen at the time of surgery, moreover the hyperthermia addiction allowed to enhance the tissue absorption, that is different depending on different factors as drugs administered and

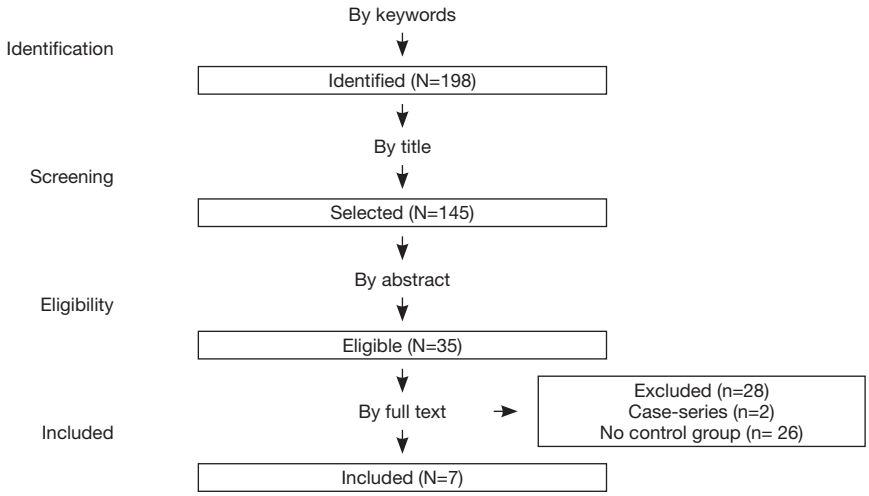

Figure 1 Study selection search strategy.

temperature reached, and consequently the cytotoxic action of chemotherapeutic drugs that reach the maximum effect between 40 and 43 centigrade (5). HIPEC treatment is adopted in different kind of cancer as gastric, colorectal and primary peritoneal carcinosis. For ovarian cancer treatment, this technique, was for a long time debated, however after the results of a randomized trial by van Driel *et al.* (6) HIPEC was inserted in NCCN guidelines as an optional treatment for interval debulking surgery (NCCN clinical practice guidelines Version 1.2019–March 8, 2019 OV-2).

The role of HIPEC in treatment of primary ovarian cancer (POC) and recurrent ovarian cancer (ROC) is actually under study. Different series could be found in literature, and different on-going trials (HORSE NCT01539785, CHORINE NCT01628380, HIPOVA-01NCT03220932). However, the heterogeneity of the population and the different drugs administered did not allow to draw definitive conclusions.

The present study aims to explore whether the addition of HIPEC in ROC patients could improve clinical outcome. A systematic review of the literature and meta-analysis was performed. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/gs-20-335).

Methods

We performed our meta-analysis following the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) (7) and the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement guidelines (supplement M1) (8). The research protocol was designed a priori, defining methods for literature search, article examination and inclusion criteria, data extraction and analysis.

Search strategy

Searches were performed using PubMed, Scopus, and Cochrane from the inception of all databases until March 2020. We searched the databases with a combination of the following keywords and Medical Subject Headings (MeSHs): "ovarian recurrence, ovarian cancer recurrence, peritoneal cancer recurrence, ovarian recurrence AND HIPEC, secondary cytoreduction HIPEC", without restricting our search geographically or linguistically. The PRISMA based flow-diagram in *Figure 1* depicts our search strategy. If it was necessary, we obtained unpublished data by contacting authors of the original papers whenever methodology indicated that further outcome data were recorded.

Study selection and outcomes

We included all studies with more than ten patients comparing women with a diagnosed first recurrent ovarian epithelial cancer treated with cytoreductive surgery and HIPEC protocols versus cytoreductive surgery without HIPEC.

Moreover, we excluded commentaries, editorials, reviews,

letters and abstracts.

Two authors (C.R. and G.R.) reviewed and classified all abstracts independently. The agreement about potential relevance was reached by consensus of the researchers; the same two authors were able to obtain full-text copies of those papers and separately extracted relevant data regarding study characteristics and outcomes. Later, the two reviewers discussed all the inconsistencies; and, if needed, a third author (S.C.) decided if no consensus was reached.

If more than one study was published on the same cohort and with the same identical endpoints, population overlapping was avoided considering only the article with the most comprehensive information.

Two different authors (G.R. and A.S.) assessed the risk of bias of all studies included in this review. The Modified Newcastle-Ottawa Scale for case-control studies was used for observational studies; The Cochrane risk of bias tool was used to assess the risk of the included RCTs. In case of disagreement, a third reviewer (S.C.) judged. Potential publication bias was assessed by the Egger's test. The articles remained were then filtered according with the availability for meta-analysis.

The primary outcome of the meta-analysis was the one-year overall survival (OS). Secondary outcomes explored were the two, three and five-year OS.

Statistical analysis

Pooled odds ratios (ORs) and 95% confidence interval (CI) were calculated using the Der Simonian and Laird random-effects model. We quantified heterogeneity to describe the percentage of total variation across studies attributable to heterogeneity rather than by chance by means of Higgins I^2-statistic. In our meta-analysis, I^2-values of 25%, 50% and 75% corresponded to cut-off points for low, moderate and high degrees of heterogeneity. We used Review Manager 5.3 (The Nordic Cochrane Centre 2014, Copenhagen, Denmark) and Stata 14.1 (Stata corp., College Station, TX, 2013) to analyze data. For studies in which the corresponding results were not shown, the Engauge Digitizer v.4.1 software was used to extract survival data obtained from the Kaplan-Meier curves.

ResultS

Study selection and study characteristics

We identified and assessed 198 initial studies (*Figure 1*). Of those, 26 studies were considered pertinent for the study criteria, seven of them were considered available for meta-analysis. Depicts summary characteristics of included studies *Table 1*. Those seven studies regarded women with ROC treated with or without HIPEC. Concerning the included studies, they were conducted in France, Spain, Italy, Israel, Brazil and Egypt between 2009 and 2019. We identified one RCT (9), one prospective (10) and five retrospective case-control studies (11-15).

Drugs used for HIPEC chemotherapy, as well as temperature and duration, were described in every study. The most used HIPEC chemotherapy was cisplatin. It was used in combination with other agents such as doxorubicin, mitomycin-C or paclitaxel. One study used carboplatin in combination with paclitaxel or doxorubicin (12). One research involved the use of oxaliplatin alone (10). Mean temperature for HIPEC was between 41–41.5 ℃.

Quality assessment of studies, with the Newcastle-Ottawa Scale and the Cochrane Tool, showed an overall good score regarding the selection and comparability of the study groups, as well as for ascertainment of the outcomes of interest in case-control studies. For the RCT (9) quality assessment revealed a low risk of bias in 5/7 analyzed elements (*Tables S1*,*S2*).

Synthesis of the results

The data are summarized in *Table 2*. In women with ROC, the use of HIPEC in addition to cytoreductive surgery and chemotherapy significantly improved 1-year OS when compared to protocols without HIPEC (OR 2.42; 95% CI, 1.06–5.56; P=0.04; I^2=4%) (*Figure 2*). The improvement in OS was maintained significant also after 2, 3 and 5 years respectively (OR 3.33; 95% CI, 1.81–6.10; P<0.01; I^2=0%), (OR 4.22; 95% CI, 2.07–8.60; P<0.01; I^2=54%), (OR 5.17; 95% CI, 1.40–19.09; P=0.01; I^2=82%) (*Figure 3*). For the primary outcome, between-studies heterogeneity was referred as low.

Publication bias

Assessment of publication bias using the Egger's regression model showed that publication bias for small studies was not present for 1-year (P=0.22), 2-year (P=0.38), 3-year (P=0.51) and 5-year (P=0.10) OS.

Perioperative mortality and complications

Regarding perioperative mortality between 1 and 30 days

Table 1 Main characteristics of studies regarding HIPEC for recurrent ovarian cancer

Characteristics	Safra T	Fagotti A	Baiocchi G	Muñoz-Casares FC	Le Brun JF	Spiliotis J	Amira G
Year	2014	2012	2016	2009	2014	2015	2019
Location	Israel	Italy	Brazil	Spain	France	Greece	Egypt
Duration	N.A.	4 years	13 years	7 years	14 years	8 years	7 years
Design	Case-control	Case-control	Case-control	Case-control	Case-control	RCT	Case-control
Sample size (HIPEC/ Non-HIPEC)	111 (27/84)	67 (30/37)	79 (20/59)	26 (14/12)	42 (23/19)	120 (60/60)	35 (15/20)
Median age (years)	HIPEC: 54.3; Non-HIPEC: 54.3	HIPEC: 51.0; Non-HIPEC: 55.0	HIPEC: 51.6; Non-HIPEC: 58.4	HIPEC: 54.0; Non-HIPEC: 54.0	N.A.	HIPEC: 58.3; Non-HIPEC: 58.1	N.A.
Cycles (number)	N.A.	N.A.	N.A.	N.A.	6	5	4
Completeness of cytoreduction (CC)	N.A.	HIPEC: CC-0 =96.7%; CC-1 =3.3%. Non-HIPEC: CC-0 =100%	HIPEC: CC-0 =79.3%; CC-1 =13.8%; CC-2 =3.4%; CC-3 =3.4%. Non-HIPEC: CC-0 =77.1%; CC-1 =12.4%; CC-3 =12.5%	HIPEC: CC-0 =64%. Non-HIPEC: CC-0 =58%	HIPEC: CC-0 =65.4%; CC-1 =17.3%; CC-2 =17.3%. Non-HIPEC: CC-0 =42.1%; CC-1 =5.2%; CC-2 =42.1%; NA =5.2%	HIPEC: CC-0 =65%. Non-HIPEC: CC-0 =55%	CC-0 and CC-1 for all cases and controls
HIPEC Technique	Closed	Closed	Closed	Open	N.A.	Open (n=40); closed (n=20)	N.A.

RCT, randomized controlled trial; Cycles, mean number of chemotherapy cycles before secondary surgery; N.A., not available.

Table 2 Survival outcomes for studies included in quantitative analysis

Author	Year	Number of patients (n) (HIPEC)	Number of patients (n) (no HIPEC)	1 y OS (n) HIPEC	1 y OS (n) no HIPEC	2 y OS (n) HIPEC	2 y OS (n) no HIPEC	3 y OS (n) HIPEC	3 y OS (n) no HIPEC	5 y OS (n) HIPEC	5 y OS (n) NO HIPEC	Median OS HIPEC (months)	Median OS non HIPEC (months)	Chemoterapy
Safra T	2014	27	84	27	81	27	79	25	67	21	38	61,6	47.7	Cisplatin + doxorubicin; carboplatin; cisplatin + mitomycin-C
Spiliotis J	2015	60	60	57	46	54	42	45	11	42	0	26.6	15.2	Cisplatin + paclitaxel
Fagotti A	2012	30	37	30	35	29	28	26	24	20	16	84	54	Oxaliplatin
Baiocchi G	2016	29	50	25	43	24	37	23	35	14	25	58.3	59.3	Cisplatin + mitomycin-C
Amira G	2019	15	20	15	20	14	17	11	13	3	7	36	38	N.A.
Muñoz-Casares FC	2009	14	12	13	12	12	12	10	3	8	2	132	60	Paclitaxel
Le Brun JF	2014	23	19	23	17	20	12	23	9	17	0	N.A.	N.A.	Carboplatin + paxitaxel; carboplatin + doxorubicin

OS, overall survival; 1 y OS, 1-year overall survival; 2 y OS, 2-year overall survival; 3 y OS, 3-year overall survival; 5 y OS, 5-year overall survival; chemotherapy, chemotherapy administered with HIPEC; N.A., not available.

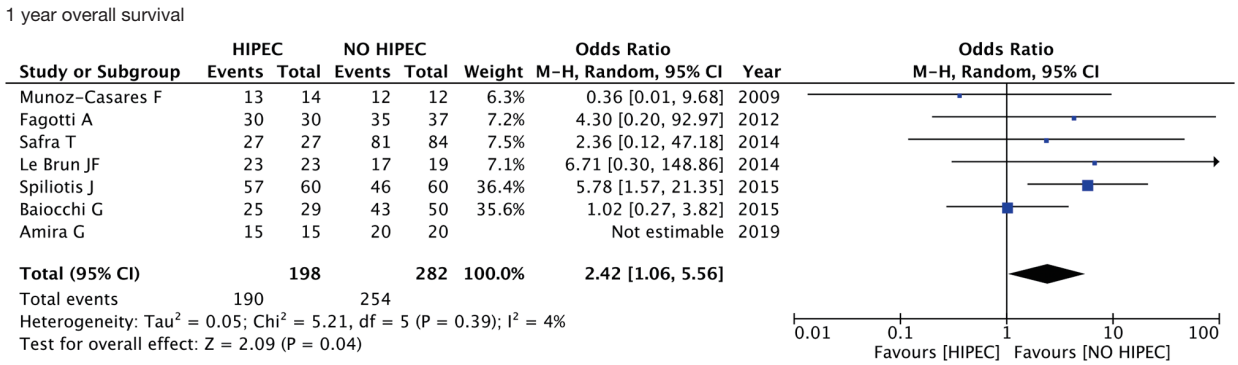

Figure 2 One-year OS forest plot

after surgery plus HIPEC, reported rates were 4% in Baiocchi *et al.* (13), 13.3% in Amira *et al.* (14) No perioperative deaths were reported in 4 studies (9-12). Post-surgical hospital stays ranged between 5.1 and 25.8 days, with a 15.9 day calculated mean.

Common adverse reactions after intervention were reported by two studies without distinction between cases and controls (11,14). Amira *et al.* (14) reported a 53% of chemotherapy-related toxicity, followed by pulmonary complications (33%) need for mechanical ventilation; 13% chest infections). Almost 20% of women experienced wound infection after surgery. The most common side effect reported by Safra *et al.* (11) was related to chemotherapy, with mild nausea which was successfully treated by anti-emetics. No complications were reported in other studies included in quantitative analysis.

Discussion

The role of HIPEC for ovarian cancer treatment, seems to furnish clear benefits. Even if the literature remains partially controversial (16).

The randomized trial conducted by van Driel *et al.* (6) demonstrated the effective role of HIPEC to prolong the survival rate of patients with diagnose of POC submitted to interval debulking surgery. However, the present study was focused on a different subset of patients affected by ROC. Actually, no concrete randomized studies are available regarding this patient's subset. An Italian randomized trial HORSE (NCT01539785) is actually in a follow-up phase, awaiting the results.

A randomized trial by Spiliotis *et al.* was published (9); however, it was not sufficient to furnish concrete conclusions about the usefulness of HIPEC for ROC.

Considering the most relevant literature available about HIPEC and ROC, in a study by Petrillo *et al.* (17), a long-term follow-up series of patients with ROC submitted to secondary cytoreductive surgery and HIPEC was studied with a median follow up of 5 and 7 years. The results of the study suggested the benefits of HIPEC in terms of long-term survival rates.

Considering our meta-analysis, the results seem very encouraging since the OS at 1, 2, 3 and 5 years were statistically significative in favor of HIPEC groups. However, the limits are related to the heterogeneity of treatments in terms of drugs used and protocol adopted for HIPEC. Moreover, surgical treatment and the achievement of complete debulking remain a fundamental step. Another limitation of our quantitative analysis is related to the design of included studies; the majority were retrospective case-control studies and only one research was a prospective randomized trial. Moreover, the small number of samples in selected studies should be taken into account.

However even, acknowledging such limitations, the results of the meta-analysis were statistically significant in favor of HIPEC, especially for the two years follow-up (P<0.0001).

In a similar meta-analysis published in 2015 by Huo *et al.* (18) the authors obtained similar conclusions. Considering this aspect, the accordance of two different studies performed in different periods reinforce the scientific evidence.

Some relevant studies reported an average of 60 months survival rate for selected patients submitted to secondary cytoreductive surgery for ovarian cancer (19,20); these data are in line with our results.

The complexity of surgery can be related to the disease dissemination influencing the surgical invasiveness and the

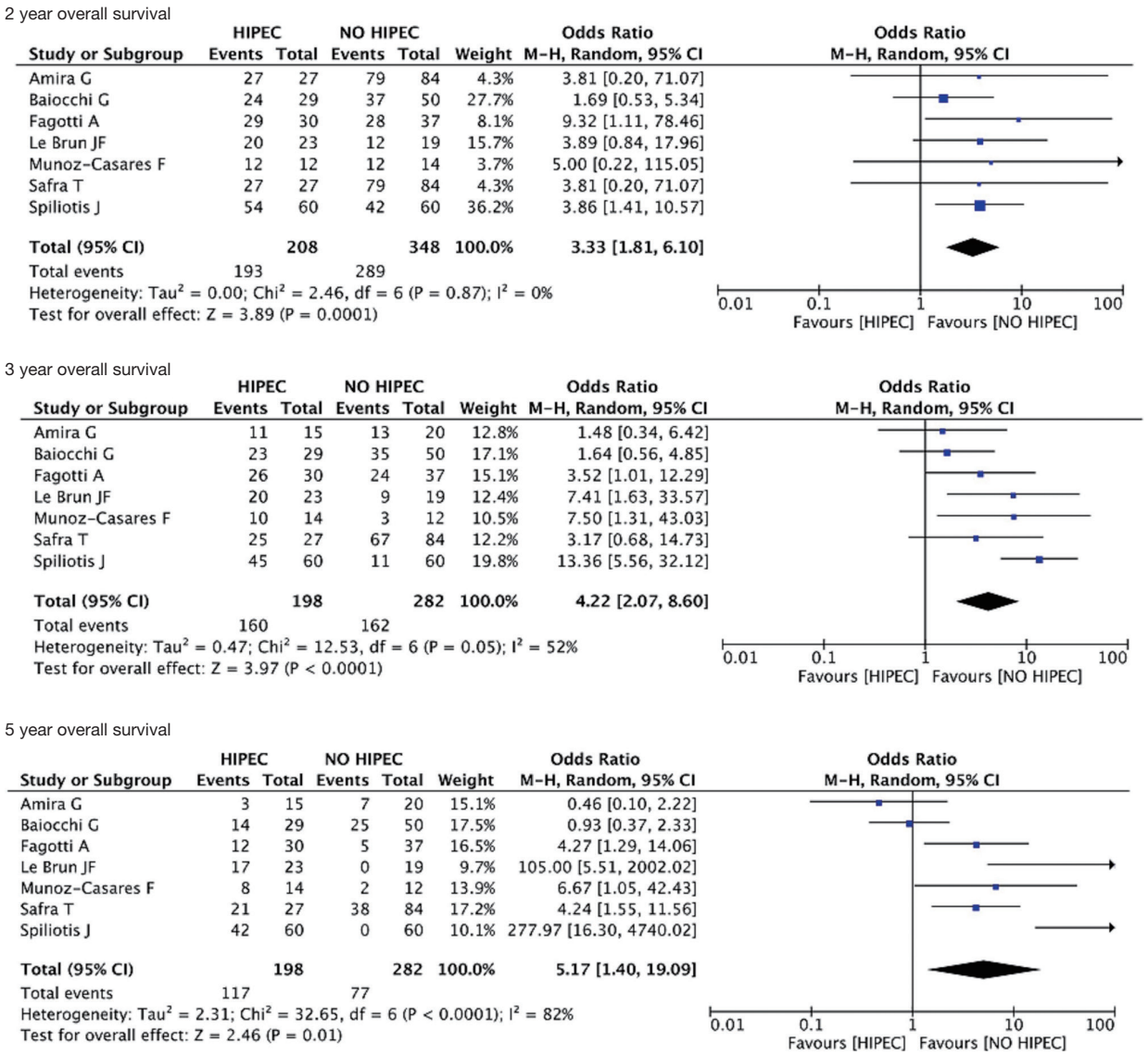

Figure 3 Two, 3, 5 years OS forest plot.

risk of complications. Considering that even if the HIPEC treatment seems to be safe in terms of intra-operative and post-operative complications; however, it represents an additional risk, especially related with bowel anastomosis leakage, often related to the number of surgical procedures performed. The surgery for ROC could be often less invasive than primary surgery (21,22), especially for isolated abdominal relapse (23), if compared with POC. In this context, the HIPEC addition during ROC, especially for isolated relapse, could reduce the risk of complications.

However, the ROC could not be the only time to perform HIPEC, in fact, as demonstrated in some studies, the HIPEC procedures can be administered even more times during the disease history (24).

Another essential aspect that should be acknowledged is the approach adopted for HIPEC administration. In a recent study by Petrillo *et al.* (25), the authors completed a pharmacokinetic study in which they demonstrated that the HIPEC drugs absorption was statistically significative enhanced in patients underwent laparoscopic procedures. Probably it was related to the enhanced intra-abdominal pressure and the reduction of pressure dispersion warrantied by laparoscopy. However, considering that the endoscopic approach is not always feasible, especially for ovarian cancer

treatment, some novel technologies are available and in an experimental phase (26-28).

Conclusions

The present systematic review and meta-analysis suggest that the HIPEC addition during cytoreductive surgery for ROC treatment can give a survival rate benefit that was recorded even after five years of follow-up.

However, the heterogeneity of the series studied cannot allow providing definitive conclusions. To date, several randomized trials are on-going with the aim to give a definitive answer to this aspect.

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Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Stefano Cianci) for the series "Ovarian Cancer Recurrence" published in *Gland Surgery*. The article was sent for external peer review organized by the Guest Editor and the editorial office.

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary

Table S1 Quality scores of the case-control studies included in the meta-analysis, assessed by the Newcastle-Ottawa scale

Author	Year	Outcome	Selection				Comparability		Exposure			Overall quality
			Case definition	Representative-ness of the cases	Selection of controls	Definition of controls	Control for the most important factor	Control for any additional factors	Ascertainment of exposure	Same method for cases and controls	Non-response rate	
Safra T	2014	Overall survival	*	*	0	0	*	*	*	*	0	6
Fagotti A	2012	Overall survival	*	*	*	*	*	*	*	*	0	8
Baiocchi G	2016	Overall survival	*	*	*	*	*	*	0	*	*	8
Muñoz-Casares FC	2009	Overall survival	*	*	0	0	*	*	0	*	0	5
Le Brun JF	2014	Overall survival	*	*	0	*	*	*	*	*	*	8

Newcastle-Ottawa scale for assessment of quality of included studies - Case-control studies (each asterisk represents if individual criterion within the subsection was fulfilled).

Table S2 Quality assessment for RCTs (method: Cochrane collaboration's tool for assessing risk of bias)

Author	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Other bias	Total
	Random sequence generation	Allocation concealment	Binding of participant and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Anything else, ideally prespecifed	Low on risk of bias
Spiliotis J	Low	Low	Low	Low	Unclear	Unclear	Low	5/7

RCTs, randomized controlled trials.