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Review

Statement of the AGO Kommission Ovar, AGO Study Group, NOGGO, AGO Austria, Swiss AGO, BGOG, CEEGOG, GEICO, and SFOG regarding the use of hyperthermic intraperitoneal chemotherapy (HIPEC) in epithelial ovarian cancer

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Summary

An international joint statement about the use of hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer was published in 2016, warning about the uncritical use of HIPEC outside controlled studies. This statement has now been updated after the most recent literature was reviewed by the participating study groups and societies. HIPEC became a treatment option in patients with advanced colon cancer after positive results of a randomized trial comparing surgery and HIPEC versus palliative treatment alone. Although this trial did not compare the added value of HIPEC to surgery alone, HIPEC for the treatment of peritoneal metastases was in the subsequent years generalized to many other cancer types associated with peritoneal carcinomatosis including epithelial ovarian cancer (EOC). In the meantime, new evidence from prospective randomized trials specifically for EOC-patients emerged, with however contradicting results and several quality aspects that made the interpretation of their findings critical. Moreover, three additional trials in colorectal cancer failed to confirm the previously presumed survival benefit through the implementation of HIPEC in peritoneally disseminated colorectal cancers. Based on a still unclear and inconsistent landscape, the authors conclude that HIPEC should remain within the remit of clinical trials for EOC-patients. Available evidence is not yet sufficient to justify its broad endorsement into the routine clinical practice.

Introduction

Hyperthermic intraperitoneal chemotherapy (HIPEC) was initially introduced as a potential treatment option for patients with peritoneal carcinosis arising from mainly gastrointestinal cancers in the late 1990's [1]. It was originally proposed in an effort to improve the efficacy of intraperitoneal (IP) chemotherapy. The rationale to expand the use of IP chemotherapy also into the treatment of epithelial advanced ovarian cancer (EOC) was based on the inherited peritoneal dissemination routes of the disease. However, in most EOC-patients with FIGO stage III or IV disease, additional retroperitoneal and extra-abdominal tumor burden coexists next to the typical peritoneally disseminated pathways, as revealed by the continuously advancing imaging techniques. This shifts the target of any therapeutic approaches also outside of the confined peritoneal cavity. In addition, adhesions formation through extensive cytoreductive techniques, often prevent the free flow of intraperitoneally infused drugs through the entire abdominal cavity. The claimed higher drug concentrations directly at the tumor site that has been used as an argument in favor of IP chemotherapy approaches, harbors the caveat that the depth of drug penetration has been shown to be restricted to a limited number of cell layers. Besides, the desired high drug concentration at the tumor site can also be equally achieved by using high-dose chemotherapy. The European Intergroup Study (HIDOC) randomized FIGO stage IIB-IV EOC-patients to multicycle high-dose chemotherapy versus standard intravenous (iv) chemotherapy following primary debulking surgery [2]. This trial failed to demonstrate any advantage of high-dose chemotherapy compared to standard iv chemotherapy (median OS in the high-dose arm 54.4 months versus 62.8 months in the control arm), providing clear evidence against the rationale of a presumed benefit through the higher dose cytotoxic chemotherapy in advanced EOC.

In accordance to these findings, IP chemotherapy is still until today not considered as standard of care in EOC despite being investigated since the 1980's [3]. There was an initial positive trial (GOG 172) almost 2 decades ago demonstrating a PFS benefit by an IP regimen compared to iv cisplatin/paclitaxel [4]. While these results were followed by a FDA alert, it is remarkable that IP chemotherapy has since failed to be widely adopted into clinical practice. This is partly because the proposed IP regimens were too toxic, and that the used control arm was outdated. Due to those caveats, numerous key opinion leaders of that time such as Gore et al. concluded that women should not be subjected to IP chemotherapy outside of controlled clinical trials to mitigate toxicity challenges [5]. Future high quality trials were warranted to enlighten two main questions: (a) what is the value of IP therapy compared to standard modern iv treatment and (b) address the issue of route of administration

for equivalent doses and schedules of the same drugs, independently from each other, but not a mosaic of these questions. The largest randomized trial ever performed on IP chemotherapy (GOG-252) has finally answered these questions and reported similar survival with iv compared to IP chemotherapy, refuting the previously reported results of the initial ip trial [6]. In this trial, 1560 patients with stage II-III ovarian cancer and residual tumor $\leq$ 1 cm after PDS were randomized. The recently reported Japanese iPOCC trial randomized 655 patients to carboplatin AUC6 iv d1 + paclitaxel 80 mg/m^2 d1,8,15 q21 versus carboplatin AUC 6 IP d1 + paclitaxel 80 mg/m^2 d1,8,15 q21 [7]. This trial showed a PFS benefit in the IP arm but failed to reach an OS difference. Of note, ~55% of the patients had residual disease of > 2 cm after surgery which was interestingly the subgroup with the highest benefit. This finding contradicts the philosophy of IP chemotherapy, as so far, the hypothesis was, that the effect is limited to patients with no macroscopic or low volume residual disease. The fact that this trial was conducted in an era before the implementation of bevacizumab or PARP inhibitors (PARPi) maintenance regimens in Japan, where the vast majority of patients were enrolled, renders its translation into modern times with modern systemic advances disputable.

Principles and origins of HIPEC

The most prevailing theory behind HIPEC is the presumed enhancement of the cytotoxic effect of chemotherapy through its intraperitoneal application. HIPEC has been used extensively in colon cancer after a randomized trial comparing surgery + HIPEC versus palliative treatment showed a positive result [8]. The main problem with the trial of Verwaal et al. was that the combination of surgery and HIPEC was compared to palliative treatment alone but not to surgery without HIPEC, which would have been the most appropriate trial design. Of note, in this trial the positive effect of the experimental arm was limited to patients with complete macroscopic resection of the tumor. This finding prompted a discussion that continued for decades, questioning whether the positive result of this trial was based on the positive effects of the actual cytoreduction alone rather than on the combination of surgery and HIPEC. In order to solve this open question, further prospective randomized trials comparing surgery versus surgery + HIPEC for colorectal cancer were initiated and some of them have been meanwhile published (*Table 1*). (1) In the PRODIGE-7 trial 265 patients with peritoneally disseminated colorectal cancers were randomized to cytoreductive surgery + HIPEC versus cytoreductive surgery alone. This trial failed to confirm the previously reported survival benefit through the addition of HIPEC, while it demonstrated a significantly higher rate long-term morbidity associated with the HIPEC arm (2) [9].

The PROPHYLOCHIP trial investigated the role of second-look surgery + HIPEC versus surveillance in patients with high risk to develop peritoneal carcinomatosis of colorectal cancer after completion of primary treatment. Again, there was no survival difference between the two study arms, while the second-look surgery + HIPEC arm was associated with excessive toxicity in the range of 41% of grade 3/4 complications [10]. Finally, the multicentre, open-label COLOPEC trial investigated the efficacy of adjuvant HIPEC in patients with locally advanced or perforated colon cancer at high risk for developing peritoneal carcinosis despite standard therapy. This study also failed to show a significant benefit towards an improved peritoneal metastasis-free survival at 18 months. [11].

Role of HIPEC in primary ovarian cancer

In the years that followed the encouraging trial results by Verwaal et al., a rather arbitrary and uncritical expansion of the indication and use of HIPEC to multiple other tumor entities, such as EOC has occurred.

Maximal effort cytoreductive surgery is the cornerstone of treatment in both primary and relapsed EOC. Prognostically most favorable, EOC-patients are those operated macroscopically

Table 1
Overview of published randomized HIPEC trials in ovarian cancer

First author	Setting of HIPEC	Drug	Sample size	Primary endpoint	PFS	OS
Lim	Primary: PDS and IDS	Cisplatin 75 mg/m^2	184	2-year PFS, but changed to PFS, but not clarified if still 2-year PFS or median PFS is intended	Negative	Negative
van Driel	Primary: IDS	Cisplatin 100 mg/m^2	245	RFS	Positive	Positive
Cascales	Primary: IDS	Cisplatin 75 mg/m^2	71		Negative	Negative
Zivanovic	Relapse: SDS	Carboplatin 800 mg/m^2	98	2-year PFS	Negative	Negative

HIPEC: hyperthermic intraperitoneal chemotherapy; PFS: progression-free survival; OS: overall survival; RFS: recurrence-free survival; PDS: primary debulking surgery; IDS: interval debulking surgery; SDS: secondary debulking surgery.

tumor-free in the upfront setting [12]. For those patients where upfront surgery is not an option due to high tumor load/spread pattern and/or co-morbidities, interval debulking surgery (IDS) following neoadjuvant chemotherapy (NACT) can be offered [13]. The rate of interval debulking surgery varies depending on the selection criteria of the institutions [14]. Recently, an overall- and PFS survival benefit was also shown for selected patients undergoing secondary cytoreductive surgery at first EOC- relapse in the prospective randomized DESKTOP III trial [15], solidifying the robust evidence around the pivotal role of high quality surgical cytoreduction in EOC [16].

In 2015, Chiva et al. presented a systematic review on HIPEC in EOC. Twenty-two publications on 1450 patients were used for the analyses [17]. In 493 patients HIPEC was applied in the first-line setting and in 957 patients at secondary debulking surgery. This systematic review of the evidence failed to demonstrate any survival benefit that justified the use of HIPEC as a standard treatment. In parallel, the first "so-called" randomized phase III trial was published by Spiliotis et al. [18]. This study reported a benefit by HIPEC, but showed significant limitations and major caveats:

- there was no description of the statistical analysis;
- there was no definition of the trials endpoints;
- patients' characteristics were imbalanced and patients' selection was arbitraty;
- the study arms had different length of follow-up and a parallel non-randomized trial in the same study centre;
- the reevaluation of the study findings by two external reviewers failed to confirm any survival benefit after extracting hazard ratios by two different methods;
- there was no information at all on patients progression-free survival;
- there was no information on surgical morbidity and mortality complications and subsequent chemotherapy treatments;
- no CONSORT flow chart was available as per good clinical practice;
- the trial was not registered.

As these major caveats were noted and publicly challenged by several others [19–21] without adequate response by the study's authors, it would be against good clinical practice and research ethos to cite this trial or use its findings as valid evidence.

A key study for HIPEC in primary EOC is the randomized OVHIPEC study reported by van Driel et al. and conducted in the Netherlands [22]. In this trial, 245 FIGO stage III EOC-patients from eight Dutch sites were randomized after three NAC cycles of carboplatin and paclitaxel between IDS + HIPEC with cisplatin 100 mg/m^2 versus IDS without HIPEC. Following IDS, all patients received 3 postoperative courses of carboplatin and paclitaxel iv. The authors reported a benefit in both PFS (14.2 vs. 10.7 months, P = 0.003) and OS (45.7 vs. 33.9 months, P = 0.02) in the HIPEC arm. In the editorial, Spriggs and Zivanovic concluded that the OVHIPEC randomized trial was a very important first step but should not drive changes in practice yet [23]. There were major criticisms that were addressed already in details in multiple publications. These included in brief:

- differences in assumed outcome data to expected results and later amendment to reduce the already small sample size;
- timing of randomization and changed timing of inclusion of the patients into the trial during recruitment;
- as the sample size was small, the difference in death events was only 15 events leading to possible bias;
- unclear strategy of the participating centers regarding allocation of surgical candidates to NAC instead of PDS;
- imbalance regarding histologic subtypes favoring the experimental arm;
- suboptimal stratification criteria;
- very long recruitment period resulting in only 3 randomized patients per center per year;
- unclear surgical qualification of the centers;
- inconsistency of the results between participating centers (no difference in outcome in the top recruiting center which recruited 105 patients (45%) of the patients and the largest effect in smaller centers);
- incomplete reporting of adverse events of systemic therapy and peri-operative complications;
- no clear definition of the pivotal in-/exclusion criteria "patients not suitable for primary debulking surgery'', which determined the study population (notably stage III only) [24,25].

Lim et al. reported on a the randomized Korean trial [26]. The major difference to the van Driel study was that HIPEC was not limited to IDS and stage III disease. Here, 184 EOC-patients with FIGO stage III and IV disease were randomized after PDS or IDS to residual tumor < 1 cm to HIPEC with intraperitoneal cisplatin 75 mg/m^2 vs. not. All patients received after surgery iv paclitaxel and carboplatin. The control arm without HIPEC included 10% more patients with FIGO stage IV disease and histologic subtypes were not categorized adequately, which makes it difficult to compare their distribution between the groups. There was a presentation at the annual meeting of the American Society of Clinical Oncology (ASCO) in 2017 showing the original primary endpoint progression-free survival rate of a phase 2 trial after 2 years [NCT01091636]. A main secondary objective was the three-year OS rate. The two-year PFS rate was 43% in both arms and the 5-year PFS rate was similar (20.9% vs. 16.0% for the HIPEC and the control arm, respectively, [not statistically significant]). The 5-year OS rate was also similar in both groups (51.0% versus 49.4%, for HIPEC and control arm, respectively). Furthermore, in the IDS group (arm similar to patients included in the Dutch OVHIPEC trial) the median PFS and OS were similar (PFS 20 versus 19 months and OS 54 versus 51 months, for HIPEC and control arm, respectively). However, data were presented as interim analysis [27]. Recently, the results after a longer follow-

up were published. Now, a median PFS of 18.8 months in the control group and 19.8 months in the HIPEC group (P = 0.43) were reported, and the median overall survival was 61.3 months in the control group and 69.5 months in the HIPEC group (P = 0.52). The primary endpoint analysis, PFS in the overall study population, with an expected PFS of 18 months in the control arm, revealed a non-significant result. Explorative subgroup analyses showed a trend in favor of HIPEC in the IDS group, but the opposite was seen in the PDS group. Of note, the statistical analysis plan was dated March 9, 2020 and only 1 analysis is mentioned, disregarding the interim analyses presented at ASCO 2017 previously.

In the PDS subgroup, the median PFS was 29.7 in the control arm versus 23.9 months in the HIPEC arm, and the median OS was not reached in the control arm and 71.3 months in the HIPEC arm. In the IDS subgroup, the median PFS was 15.4 months in the control arm (n = 43) and 17.4 months in the HIPEC arm (n = 34) (HR 0.60; 95% CI, 0.37–0.99; P = 0.04), while the median OS was 48.2 months in the control arm and 61.8 months in the HIPEC arm (HR 0.53; 95% CI, 0.29–0.96; P = 0.04). Originally, the trial aimed to show a HR of 1.6 and it was calculated that 168 patients are needed to test with a type 1 error = 0.05, 2-sided at a power of 80%. It is unclear why, but the first documented trial version in NCT registry describes a sample size of 214. In June 2013 this was changed to HR of 1.33 and the sample size was corrected to 170 patients and in the meantime the trial phase was changed from phase 2 to phase 2/3. Two years later another modification of the type 1 error to 0.2 1-sided and a power of 80% was performed. Now the planned sample size was 184. Four years after the end of the recruitment and three years after the first presentation at ASCO, there was another modification of the sample size calculation in 2020: it was assumed that the median survival time is 1.5 years for the control arm and 2.0 years for the HIPEC arm, which conveys to a HR of 0.75. A log-rank test with a total sample size of 184 subjects (per each group 92 subjects) achieves 82.3% power at a one-sided 0.20 significance level to detect an HR of 0.75. It was additionally calculated that a log-rank test with the sample size of 184 subjects achieves 68.8% power at one-sided 0.1 significance level to detect a HR of 0.75.

According to the study protocol and to clinicaltrials.gov the primary endpoint is still 2-year PFS and 3-year OS. The recent publication now describes that a log-rank test with an overall sample size of 184 achieves 55.1% and 81.0% power at a $P < 0.05$ significance level to detect hazard ratios (HRs) of 0.75 and 0.66 when median survival time of the control group is 18.0 months. In addition, in 2012 an amendment was filed for an interim analysis after enrollment of 50% of the patients: "At the interim analysis, a statistical test will be performed. The nominal significance levels will be determined later. The exact nominal significance level will be determined based on the exact number of events at the time of the interim analysis. The stopping boundaries will be calculated using an O'Brien-Fleming error spending function." Unfortunately, this interim analysis is unknown to the authors and the used significance levels and alpha spending rules including its impact on the final analysis and interpretation of the data. If the ASCO presentation was an additional second interim analysis, then there were two interim analyses neglecting a mandatory alpha spending.

Interestingly, HIPEC lead to a critical prolongation of the median time of surgery from 405 minutes to 525 minutes and a substantial increased rate of surgical complications: rate of bowel leakage/fistula/perforation increased from 0 to 7.6%.

Despite these limitations, the study by Lim et al. confirmed the lack of PFS- or OS benefit in the ITT population of advanced EOC through the additional use of HIPEC at maximal effort cytoreduction (P = 0.43).

A major point that would need to be addressed is that both above-mentioned randomized HIPEC trials in EOC share the common limitation of a substandard use of the, nowadays standard, maintenance targeted regimens with bevacizumab and/or PARPi. There is a well-defined significant OS benefit in patients at high risk for relapse through the addition of bevacizumab [mean survival time 39.3 versus 34.5 months]. Even though all patients undergoing IDS are classified to be at high risk [28,29], none of them was received bevacizumab in addition to chemotherapy in the two prospective HIPEC trials.

Cascales et al. [30] recently published results of a single center phase 3 trial evaluating disease-free survival as primary endpoint in patients undergoing cytoreductive surgery with HIPEC after NAC. The trial recruited 71 patients in a time period of approximately 7 years. Median PFS and OS were 12 and 45 months versus 18 and 52 months in the control and experimental groups, respectively (both not significant). This negative trial was criticized as there were major limitations regarding the sample size, the reporting and interpretation of the data [31–35].

Role of HIPEC in relapsed ovarian cancer

There is up to date no randomized phase III trial investigating the role of HIPEC in recurrent ovarian cancer. However, there is a large randomized phase II trial published by Zivanovic et al. [36]. Relapsed EOC-patients undergoing secondary cytoreductive surgery were randomized to HIPEC with carboplatin versus no HIPEC. The median PFS was 12.3 months in the HIPEC arm versus 15.7 months in the control arm (P = 0.05) and median OS was 52.5 versus 59.7 months (P = 0.31).

As there is only 1 randomized trial in relapsed ovarian cancer, which was negative, the use of HIPEC cannot be supported outside of controlled trials.

Conclusion

The here presented trial landscape around the evidence of HIPEC in addition to cytoreduction for advanced EOC is not sufficient or

Table 2
Overview of ongoing phase 3 trials of HIPEC in Ovarian Cancer with a sample size of at least 100 patients

NCT/Name	Setting	Drug	Sample size	Primary endpoint	Status	Sponsor
03842982/CHIPPI-1808	Primary: PDS and IDS	Cisplatin 100 mg/m^2	362	DFS	Recruiting	Centre Oscar Lambret
03772028/OVHIPEC-2	Primary: PDS	Cisplatin	538	OS	Recruiting	The Netherlands Cancer Institute
03373058/EHTASEOCCS	Primary: PDS and IDS	Docetaxel 75 mg/m^2 +cisplatin 75 mg/m^2	310	DFS	Recruiting	Affiliated Cancer Hospital & Institute of Guangzhou Medical University
03180177/EHNPCTASEOC	Primary: IDS	Paclitaxel 175 mg/m^2 +cisplatin 75 mg/m^2 as cycle 1 and at IDS	263	Response Optimal surgery DFS	Not yet recruiting	Shu-Zhong Cui
03220932/HIPOVA-01	Relapse: platinum resistant IDS at cycle 4	Cisplatin 70 mg/m2	132	PFS	Not yet recruiting	Hospices Civils de Lyon
01376752/CHIPOR	Relapse: after 2nd line platinum	Cisplatin 75 mg/m2	415	OS	Active, not recruiting	UNICANCER
04473339	Relapse	Lobaplatin 30 mg/m^2	280	PFS	Recruiting	CAI Hongbing
03371693/HIPECOV	Primary + relapse	Lobaplatin 30 mg/m^2	112	OS	Active, not recruiting	Zhongnan Hospital

PDS: primary debulking surgery; IDS: interval debulking surgery; DFS: disease-free survival; OS: overall survival; PFS: progression-free survival.

adequate enough to change the standard of care, which remains maximal effort cytoreductive surgery and iv chemotherapy plus targeted maintenance treatment. Similarly, available evidence is lacking to establish HIPEC as standard of care in relapsed ovarian cancer. As HIPEC may convey substantial toxicity, its use should be limited to ongoing prospective trials (*Table 2*). This estimation of the available evidence is congruent to the last ESMO/ESGO consensus meeting in 2018 [3]. The high number of ongoing HIPEC trials in EOC clearly indicates, that also the supporters of HIPEC see a need to generate adequate evidence, before broad implementation of this treatment option into daily clinical routine, an intention that needs to be congratulated. Most recently, the Ovarian Cancer Consensus Conference on Clinical Research of the Gynecologic Cancer Intergroup (GCIG) established that HIPEC cannot be used as a control arm in current and future clinical trials, reinforcing our interpretation of current evidence [37]. Future trials should be of large scale to avoid bias by for example randomizing double blind HIPEC versus heated saline and assigning the arms after completion of the cytoreductive effort and not before. Moreover, the so far limitations of lacking modern systemic therapy, as standard treatment should not be repeated in any newly designed HIPEC trials. Even though bevacizumab is now approved since more than ten years for primary ovarian cancer, its role in the published HIPEC trials is not clear. In view of the overwhelming data about the benefit of PARPi for ovarian cancer patients [38–40], these drugs, alone or in the combination with bevacizumab, should be offered as maintenance therapy in future HIPEC trials. In general, the standard arm of a trial should always include the best available therapy to provide meaningful results and to increase the chance of acceptance of results within the academic community. In agreement with our previous joint statements presented to the scientific community in 2013 and 2016 about the use of HIPEC in EOC [41,42], we also now, a decade later, continue to see no high quality, adequate evidence to justify the broad implementation of HIPEC in the clinical practice of advanced and relapsed EOC outside of well-designed clinical trials.

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References

[1] Fujimoto S, Shrestha RD, Kobayashi K, et al. Combined treatment with surgery and intraperitoneal hyperthermic perfusion (IPHP) for far-advanced gastrointestinal cancer with peritoneal seeding. Acta Med Austriaca 1989;16(3–4):76–80.

[2] Möbus V, Wandt H, Frickhofen N, Bengala C, Champion K, Kimmig R, et al. Phase III trial of high-dose sequential chemotherapy with peripheral blood stem cell support compared with standard dose chemotherapy for first-line treatment of advanced ovarian cancer: intergroup trial of the AGO-Ovar/AIO and EBMT. J Clin Oncol 2007;25(27):4187–93.

[3] Colombo N, Sessa C, du Bois A, et al. ESMO-ESGO consensus conference recommendations on ovarian cancer: pathology and molecular biology, early and advanced stages, borderline tumours and recurrent disease. Int J Gynecol Cancer 2019. http://dx.doi.org/10.1136/ijgc-2019-000308 [ijgc-2019-000308. Online ahead of print].

[4] Armstrong DK, Bundy B, Wenzel L, et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N Engl J Med 2006;354(1):34–43.

[5] Gore M, du Bois A, Vergote I. Intraperitoneal chemotherapy in ovarian cancer remains experimental. J Clin Oncol 2006;24:4528–30.

[6] Walker JL, Brady MF, Wenzel L, Fleming GF, Huang HQ, DiSilvestro PA, et al. Randomized trial of intravenous versus intraperitoneal chemotherapy plus bevacizumab in advanced ovarian carcinoma: an NRG oncology/gynecologic oncology group study. J Clin Oncol 2019;37(16):1380–90.

[7] Fujiwara K, Nagao S, Yamamoto K, et al. A randomized phase 3 trial of intraperitoneal versus intravenous carboplatin with dose-dense weekly paclitaxel in patients with ovarian, fallopian tube, or primary peritoneal carcinoma (a GOTIC-001/JGOG-3019/GCIG, iPocc trial). Presented at annual meeting of the Society of gynecologic oncology (SGO) in 2022.

[8] Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol 2003;21(20):3737–43.

[9] Quénet F, Elias D, Roca L, et al. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy versus cytoreductive surgery alone for colorectal peritoneal metastases (PRODIGE 7): a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2021;22(2):256–66.

[10] Goéré D, Glehen O, Quenet F, et al. Second-look surgery plus hyperthermic intraperitoneal chemotherapy versus surveillance in patients at high risk of developing colorectal peritoneal metastases (PROPHYLOCHIP-PRODIGE 15): a randomised, phase 3 study. Lancet Oncol 2020;21(9):1147–54.

[11] Klaver CEL, Wisselink DD, Punt CJA, et al. Adjuvant hyperthermic intraperitoneal chemotherapy in patients with locally advanced colon cancer (COLOPEC): a multicentre, open label, randomised trial. Lancet Gastroenterol Hepatol 2019;4(10):761–70.

[12] du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the arbeitsgemeinschaft gynaekologische onkologie studiengruppe ovarialkarzinom (AGO-OVAR) and the Groupe d'investigateurs nationaux Pour les études des cancers de l'ovaire (GINECO). Cancer 2009;115(6):1234–44.

[13] Vergote I, Tropé CG, Amant F, et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med 2010;363(10):943–53.

[14] Vergote I, du Bois A, Amant F, Heitz F, Leunen K, Harter P. Neoadjuvant chemotherapy in advanced ovarian cancer: On what do we agree and disagree? Gynecol Oncol 2013;128(1):6–11.

[15] Harter P, Sehouli J, Vergote I, et al. Randomized trial of cytoreductive surgery for relapsed ovarian cancer. N Engl J Med 2021;385(23):2123–31.

[16] Querleu D, Planchamp F, Chiva L, et al. European society of gynaecological oncology (ESGO) guidelines for ovarian cancer surgery. Int J Gynecol Cancer 2017;27(7):1534–42.

[17] Chiva LM, Gonzalez-Martin A. A critical appraisal of hyperthermic intraperitoneal chemotherapy (HIPEC) in the treatment of advanced and recurrent ovarian cancer. Gynecol Oncol 2015;136(1):130–5.

[18] Spiliotis J, Halkia E, Lianos E, et al. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol 2015;22:1570–5.

[19] Harter P, Reuss A, Sehouli J, Chiva L, du Bois A. Brief report about the role of hyperthermic intraperitoneal chemotherapy in a prospective randomized phase 3 study in recurrent ovarian cancer from spiliotis et al.. Int J Gynecol Cancer 2017;27(2):246–7.

[20] Sanz Rubiales A, Del Valle MA. Survival analysis in a randomized trial of HIPEC in ovarian cancer. Ann Surg Oncol 2017;24(Suppl 3):631.

[21] Batista TP. Comment on: surgery and hipec in recurrent epithelial ovarian cancer: a prospective randomized phase III study. Ann Surg Oncol 2017;Dec;24(Suppl 3):630.

[22] van Driel WJ, Koole SN, Sikorska K, et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med 2018;378:230–40.

[23] Spriggs DR, Zivanovic O. Ovarian cancer treatment – are we getting warmer? N Engl J Med 2018;378:293–4.

[24] Fotopoulou C, Sehouli J, Mahner S, et al. HIPEC: HOPE or HYPE in the fight against advanced ovarian cancer? Ann Oncol 2018;29(8):1610–3.

[25] Vergote I, Harter P, Chiva L. Is there a role for intraperitoneal chemotherapy, including HIPEC, in the management of ovarian cancer? J Clin Oncol 2019;37(27):2420–3.

[26] Lim MC, Chang SJ, Park B, et al. Survival after hyperthermic intraperitoneal chemotherapy and primary or interval cytoreductive surgery in ovarian cancer: a randomized clinical trial. JAMA Surg 2022;157(5):374–83.

[27] Lim MC, Chang S-J, Yoo HJ, et al. Randomized trial of hyperthermic intraperitoneal chemotherapy (HIPEC) in women with primary advanced peritoneal, ovarian, and tubal cancer. J Clin Oncol 2017;35 [https://meetings.asco.org/abstracts-presentations/153316. suppl; abstr 5520].

[28] Oza AM, Cook AD, Pfisterer J, et al. Standard chemotherapy with or without bevacizumab for women with newly diagnosed ovarian cancer (ICON7): overall survival results of a phase 3 randomised trial. Lancet Oncol 2015;16(8):928–36.

[29] Harter P, Mouret-Reynier MA, Pignata S, et al. Efficacy of maintenance olaparib plus bevacizumab according to clinical risk in patients with newly diagnosed, advanced ovarian cancer in the phase III PAOLA-1/ENGOT-ov25 trial PAOLA 1. Gynecol Oncol 2022;164(2):254–64.

[30] Antonio CCP, Alida GG, Elena GG, et al. Cytoreductive surgery with or without HIPEC after neoadjuvant chemotherapy in ovarian cancer: a phase 3 clinical trial. Ann Surg Oncol 2022;29(4):2617–25.

[31] Chiva L, Harter P, Boria F, Ramirez P. A comment on a recent failed HIPEC trial. Ann Surg Oncol 2022;29(5):3359–60.

[32] Carneiro VCG, Ramalho NM. Letter to the Editor: comment on "cytoreductive surgery with or without HIPEC after neoadjuvant chemotherapy in ovarian cancer: a phase 3 clinical trial". Ann Surg Oncol 2022;29(5):3351–2.

[33] Raghavan S, Patel S, Prem A, Pandey D. Enigma of hyperthermic intraperitoneal chemotherapy with interval cytoreduction surgery: need to push more boundaries! Ann Surg Oncol 2022;29(5):3355–6.

[34] Noiret B, Bakrin N, Eveno C. Combining HIPEC to interval surgery in ovarian cancer? One step forward with a second randomized study: comment on "cytoreductive surgery with or without hipec after neoadjuvant chemotherapy in ovarian cancer-a phase 3 clinical trial". Ann Surg Oncol 2022;29(5):3357–8.

[35] Paulino E, Melo AC. The debatable role of HIPEC in ovarian cancer. Ann Surg Oncol 2022;29(5):3353–4.
[36] Zivanovic O, Chi DS, Zhou Q, et al. Secondary cytoreduction and carboplatin hyperthermic intraperitoneal chemotherapy for platinum-sensitive recurrent ovarian cancer: an MSK team ovary phase II study. J Clin Oncol 2021;39(23):2594–604.
[37] Vergote I, Gonzalez-Martin A, Lorusso D, et al. Clinical research in ovarian cancer: consensus recommendations from the Gynecologic Cancer InterGroup. Lancet Oncol 2022;23:e374–84.
[38] Moore K, Colombo N, Scambia G, et al. Maintenance Olaparib in patients with newly diagnosed advanced ovarian cancer. New Engl J Med 2018;379:2495–505.
[39] Gonzalez-Martin A, Pothuri B, Vergote I, et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. New Engl J Med 2019;381:2391–402.
[40] Ray-Coquard I, Pautier P, Pignata S, et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. New Engl J Med 2019;381:2416–28.
[41] Harter P, Mahner S, Hilpert F, et al. Statement by the Kommission OVAR of the AGO study group on the use of HIPEC (hyperthermic intraperitoneal chemotherapy) to treat primary and recurrent ovarian cancer. Geburtshilfe Frauenheilkd 2013;73(3):221–3.
[42] Harter P, du Bois A, Mahner S, et al. Statement of the AGO Kommission Ovar, AGO study group, NOGGO, AGO Austria and AGO Switzerland regarding the use of hyperthermic intraperitoneal chemotherapy (HIPEC) in ovarian cancer. Geburtshilfe Frauenheilkd 2016;76(2):147–9.