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Logoregional Treatment Hipec in the Management of Peritoneal Metastasis from Ovarian Cancer

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Abstract

The standard of care in epithelial ovarian cancer is complete surgical cytoteduction followed by systemic chemotherapy.

The 30 % of patients even after this treatment are relapsed. The 2nd line treatment includes logo regional management with intraperitoneal chemotherapy.

The aim of this article is to focuses in IP treatments with HIPEC.

Introduction

Epithelial ovarian cancer (EOC) is the deadliest gynecologic malignancy **[**1**]**. The majority of women are diagnosed at advanced stage with widely metastatic peritoneal disease. Standard of care involves a combination of surgery and chemotherapy. The ability to surgically resect tumors with optimal cytoreduction surgery (CRS), ideally to no gross residual disease (R0), is an important positive prognostic factor **[**2**]**. Despite the improvements seen in median survival time with the current standard of radical tumor CRS and IV carboplatin and paclitaxel, long term survival rates for patients with advanced epithelial ovarian carcinoma remain disappointing and efforts continue to develop more effective primary therapy.

One of the reasons that Intraperitoneal (IP) chemotherapy has been proposed for advanced ovarian cancer is that ovarian cancer typically spreads intraperitoneally. However, retroperitoneal disease and, according to newer imaging techniques, extra-abdominal disease are present in the majority of patients with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease. In addition, adhesions, which are frequently observed after debulking surgery, prevent the spread of the drugs in the abdominal cavity. Furthermore, a higher drug concentration going directly to the tumor has been used as an argument for ip chemotherapy. However, the depth of drug penetration has been shown to be restricted to a limited number of cell layers.

For most patients with EOC, the majority of disease burden is in the peritoneal cavity and can be quantified by the peritoneal cancer index (PCI) **[**3**]**. The PCI is a measure of the extent of disease burden in the peritoneal cavity. Due to this location, normothermic IP chemotherapy has been studied in prospective clinical trials in the post-operative treatment of primary EOC, and NCCN has noted the combined IV/IP regimen as preferred regimen for optimally cytoreduced Stage III EOC. In the setting of recurrence, treatment guidelines are determined by the time to recurrence and location of metastatic disease.

HIPEC during CRS for EOC has been gaining more attention in the treatment of metastatic peritoneal disease. Specifically, HIPEC has more frequently been utilized in the recurrent setting with secondary CRS, but recent studies have evaluated its role in primary management of ovarian cancer.

The aim of this article is to review previous and ongoing studies regarding the use of HIPEC in context of the overall use of IP chemotherapy for the treatment of EOC.

Intraperitoneal chemotherapy (normothermic)

In normothermic IP chemotherapy, cisplatin and paclitaxel are injected into the patient's peritoneal cavity through an intraabdominal port. IP chemotherapy is administered in the post-operative period over a course of up to six cycles. Three large prospective randomized studies support the use of IP chemotherapy in the primary treatment of EOC. In the Gynecologic Oncology Group (GOG) 104 study, patients were randomized to two arms: the control arm of cisplatin and cyclophosphamide IV and the experimental arm of cisplatin IP and cyclophosphamide IV. While there was a statistically significant overall survival (OS) benefit to the IP regimen of 49 months in comparison to 41 months for the IV regimen, consensus was the benefits of IP chemo are not greater than the benefits of new agent paclitaxel **[**4**]**. In GOG 114, patients in the control arm received six cycles of cisplatin and paclitaxel IV with an OS of 52.5 months and the experimental arm received two cycles of carboplatin IV, followed by six cycles of cisplatin and paclitaxel IP with an OS of 63.2 months. Progression free survival (PFS) and OS were statistically significant, but were partially attributed to the addition of two extra cycles of chemotherapy in the IP arm **[**5**]**.

GOG 172 influenced practice patterns in the United States. The IV/IP regimen of IP cisplatin and paclitaxel, plus IV paclitaxel demonstrated the longest median OS compared to IV carboplatin and paclitaxel in patients with optimally cytoreduced stage III ovarian cancer. The median PFS for the IV alone and IV/IP regimens was 18.3 and 23.8 months, respectively. The median OS for the IV and the IP regimens was 49.7 and 66.9 months, respectively. Due to chemotherapy-associated toxicities, only 42% of women on the IP regimen actually received six cycles of therapy, and 49% received three or fewer IP cycles **[**6**]**. Because the OS benefit outweighed the toxicity of the regimen, the NCI Clinical Announcement recognized the superiority of IP chemotherapy in the optimal disease setting **[**7**]**.

In a follow up analysis of the mature data of GOG 114 and GOG 172 combined, an OS benefit remains significant for IP regimens after 10 years of follow up. This benefit in OS was most pronounced in patients who underwent optimal CRS to R0 treated with the IP regimen. Specifically, in GOG 172, the OS was 127 months in this subset of patients **[**8**]**. There was also a correlation noted between survival

and the number of IP cycles completed in a separate follow up analysis [9]. A more recent large prospective trial, GOG 252, compared weekly IV chemotherapy regimens to varying dose reduced IP regimens. All arms of the trial had bevacizumab added during treatment and as maintenance. No significant differences in PFS were observed between the three arms. In comparison to GOG 172, more patients were able to complete the IP regimens, but all arms had excessive toxicity. One concern in interpreting the data from GOG 252 is the addition of bevacizumab to all arms could have influenced the results and analysis [10]. With the inability to replicate the results from GOG 172 and the limitation to access IP chemotherapy outside of the tertiary setting, there has been increased interest in HIPEC as a treatment alternative in the primary and recurrent ovarian cancer setting.

HIPEC

In HIPEC, heated intraabdominal chemotherapy is administered at the end of CRS. HIPEC has several potential benefits. High-dose chemotherapy can be used because the plasma-peritoneal barrier results in little absorption into the blood stream [11,12]. In addition, there is higher peritoneal penetration in comparison to IV regimen, and HIPEC does not have the limitation of traditional IP regimen of post-operative adhesions [13,14]. Hyperthermia itself has cytotoxic effects and can increase the depth of tumor penetration by the chemotherapeutic agent up to 3 mm and moreover can potentiate its antineoplastic effects [15–18].

A major limitation to HIPEC is the previously reported morbidity and mortality and thus its use was often discouraged [19]. To proceed with HIPEC, CRS to R0, CC0 (non-visible disease remaining) or CC1 (less than 2.5 mm visible disease remaining) is required and involves radical and complex surgeries that are associated with higher complication rates. Currently, particularly in high-volume centers with HIPEC specialists, morbidity and mortality has drastically improved [20,21].

One large retrospective review of 694 patients, treated between 2005 and 2011, utilizing the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQUIP) database, demonstrated a complication rate of 33% and 30-day mortality of 2.3%, both rates consistent with outcomes for other major complex abdominal operations [21].

In 2015, Chiva et al reported a systematic review of HIPEC in ovarian cancer. Twenty-two publications with 1450 patients were used for the analyses [22]. In 493 patients, HIPEC was used in the first-line setting, and in 957 patients, it was used at the time of secondary debulking surgery. The authors concluded that their systematic review had failed to show a survival benefit that justified the use of HIPEC as a standard daily practice.

HIPEC as upfront treatment of ovarian cancer

The largest prospective randomized clinical trial demonstrated a survival advantage for patients who received HIPEC, compared to standard IV chemotherapy, for the treatment of primary EOC. (Table 1) All patients received neoadjuvant chemotherapy after determining they were not eligible for primary CRS and had to have at least stable disease after receiving up-front IV chemotherapy. The control arm received standard IV chemotherapy before and after CRS (PFS = 10.7 months, OS = 33.9 months). The experimental arm received the same standard IV chemotherapy but also received HIPEC with cisplatin during CRS (PFS = 14.2 months (p = 0.01), OS = 45.7 months (p = 0.02)). Over 90% of patients completed full six cycles of IV chemotherapy in both arms **[**23**]**.

While the PFS and OS in this trial are shorter than the previous mentioned normothermic IP trials, it should be noted that this is a different patient population. The PFS and OS survival in the control arm of this trial are similar to established data in patients receiving NACT and interval CRS **[**24**]**.

Similarly, a large retrospective study from Italy showed improved outcomes in patients who underwent HIPEC after having a complete or partial response to neoadjuvant IV chemotherapy in comparison to HIPEC at primary CRS. **[**25,26**]** In addition to standardizing the HIPEC procedure, the time of administration of HIPEC is another important factor.

Author	Study type	N[1]	Chemotherapy	PFS	OS
Van Driel et.al	Prospective	245	Cisplatin	14.2 months	45.7 months
Bakrin et. al	Retrospective Cohort	92	Cisplatin (80%)[2]	n/a	CCo: 41.5 months
Gonzalez Bayon et.al	Prospective	15	Cisplatin and Doxorubicin	n/a	77.8 months
Cascales-Compos et al.	Retrospective Series	52	Paclitaxel	1 year: 81% 3 years: 63%	n/a
Bae et al	Retrospective Case Control	67	Carboplatin or Paclitaxel	3 years: 56.3%	3 years: 66.1%

1: Number of HIPEC patients in trial. 2: Chemotherapy included in analysis: included cisplatin, doxorubicin, oxaliplatin, mitomycin, cisplatin and mitomycin, and cisplatin and doxorubicin.

Table 1. HIPEC primary trials.

A retrospective cohort study from France looked at 92 patients receiving HIPEC for primary EOC treatment. The majority (60.8%) received consolidation HIPEC treatment after receiving 6–9 cycles of IV carboplatin and paclitaxel. The rest received HIPEC at primary CRS (13%) and at interval CRS (26.1%.) The majority of patients received cisplatin HIPEC (80.4%,) but 35.9% did receive a second

agent with HIPEC, either doxorubicin (19.6%) or mitomycin (18.5%). Significant to survival were timing of HIPEC, peritoneal cancer index (PCI), and R0 CRS. Longest median OS was seen in the primary CRS group at 52.7 months, followed by interval CRS at 36.5 months and then consolidation HIPEC at 33.4 months ($p = 0.03$.) Of all primary HIPEC patients, those able to be optimally cytoreduced to less than 2.5 millimeters (mm) had a median survival of 41.5 months compared to 21.2 months with residual disease greater than 2.5 mm ($p < 0.01$) **[**27**]**. Again, this is a different patient population than was evaluated in previous normothermic IP trials; therefore we cannot make direct comparisons.

HIPEC in the Treatment of Recurrent Ovarian Cancer

Substantially more studies have been published regarding the use of HIPEC in the management of recurrent ovarian cancer.

Although, a significant amount are retrospective, evaluating a small series of patients or inconsistent with patient parameters and HIPEC dosing. Platinum agents are one of the most commonly used during HIPEC for ovarian cancer, but the dose varies in trials.

A phase I trial was published regarding the maximum tolerated dose of (MTD) of cisplatin for HIPEC at time of first recurrence (Table 2).

The Mitomycin dose MTD established were 100 mg/m2 with 25% of patients experiencing Gr 3–4 toxicity. Notably no severe hematologic toxicity at this dose, and over 90% of patients completed all 6 cycles of adjuvant IV chemotherapy. The median PFS of 13.6 months was comparable to previously published PFS in recurrent ovarian patients treated with IV chemotherapy alone. Peritoneal platinum concentration was significantly elevated in comparison to plasma levels, and platinum DNA adducts were found in tumor biopsies after HIPEC confirming cytotoxic activity immediately after a single dose of cisplatin. A Phase II trial is currently open to further evaluate the efficacy of this dose and regimen **[**28**]**.

Author	Study type	N[1]	Chemotherapy	PFS	OS
Zivanovic et. al	Phase I Prospective	12	Cisplatin	13.6 months	n/a
Bakrin et. al	Retrospective Cohort	470	Cisplatin (76%)[2]	n/a	CCo: 51.5 months 1st recurrence: 62.8 months
Gonzalez Bayon et.al	Prospective	27	Cisplatin and Doxorubicin	n/a	2nd recurrence: 35.7 months
Cascales-Compos et al. Fagotti et.al Spiliotis et. al	Case Control Case Control Prospective	39 30 60	Paclitaxel Oxaliplatin Multiagent[3]	21 months 26 months n/a	n/a 5 years: 42.7% 26.7 months

1: Number of HIPEC patients in trial.

2: Chemotherapy included in analysis: included cisplatin, doxorubicin, oxaliplatin, mitomycin, cisplatin and mitomycin, and cisplatin and doxorubicin.

3: Chemo-sensitive-Cisplatin and paclitaxel; Chemo-resistant-Doxorubicin with paclitaxel or mitomycin

Table 2. HIPEC recurrent trials in ovarian cancer.

A prospective trial from Greece evaluated the role of HIPEC at first recurrence. Sixty patients were randomized to each arm; CRS followed by IV chemotherapy versus CRS with HIPEC followed by IV chemotherapy. The trial included both chemo-sensitive and chemo-resistant patients. The HIPEC chemo-sensitive patients were treated with cisplatin and paclitaxel during CRS and the chemo-resistant were treated with doxorubicin and paclitaxel or mitomycin. Mean OS was 26.7 months in the HIPEC group versus 13.4 months in the control group ($p < 0.01$.) The OS was similar in both the HIPEC chemo-sensitive (26.8 months) and chemo-resistant (26.6 months) subgroups. In comparison, the OS was significantly different in the control arm chemo-sensitive (15.2 months) and chemo-resistant (10.2months) subgroups ($p<0.01$.) Both arms achieved similar rates of CCo CRS. However, the overall survival in the HIPEC CC0 group was significantly higher (30.9 months) than the control CCo group (16.9 months) **[**29**]**.

A similar patient population was studied in Italy. A case control study with 37 patient controls receiving either CRS and IV chemotherapy (13 patients) or IV chemotherapy alone (24 patients) versus 30 patients undergoing CRS and HIPEC. All patients were experiencing a first recurrence, and the initial PFS was similar in both the control and case arms. The only significant difference between the arms was pattern of recurrence. The control arm had significantly more patients with single nodule or localized recurrence. All control patients achieved CC0 CRS, and 96.7% of HIPEC patients achieved

CC0 CRS. PFS was 15 months in the control arm and 26 months in the HIPEC arm. Interestingly, over half of the HIPEC patients had a longer secondary PFS after HIPEC than the primary PFS after Cancers 2018, 10, 296 6 of 10 initial treatment. The HIPEC patients had significantly longer OS, secondary PFS, and deaths than the control group [30].

Discussion

Ovarian cancer is the deadliest gynecologic malignancy in the United States. Normothermic IP chemotherapy for primary EOC has a known benefit in the optimal CRS setting. Unfortunately, widespread use has not occurred due to concern for toxicity and patient access to tertiary care centers. Due to these concerns, there is interest in HIPEC therapy for the management of primary and recurrent EOC. The largest HIPEC study published to date was in the setting of primary EOC. A survival benefit in patients undergoing interval CRS was found with the addition of HIPEC, and there was no difference in toxicity between the control and HIPEC arms [22]. A critique of the study is that it did not have an IP chemotherapy arm for comparison. The role of normothermic IP chemotherapy is unclear in the interval CRS patient population. A phase II randomized trial, OV21/PETROC, was completed and the IPregimenwasfoundtobewelltoleratedwithreasonabletoxicityandnoreductioninQOL.Therewas a noted decrease in progression of disease at nine months in the IP group, however, as the study was underpowered, there was no difference found in PFS and OS between the IV and IP arms [31].

In conclusion, there is now high quality prospective data suggesting a survival benefit to HIPEC therapy for patients undergoing primary treatment of EOC after receipt of neoadjuvant chemotherapy and optimal cytoreduction. Poorer quality data exists supporting its use in other clinical contexts such as recurrent disease. This treatment has not been studied in multiple clinical contexts, the regimen and toxicity management has not been standardized and HIPEC has not yet been compared to other standard treatments such as normothermic IP chemotherapy. Therefore, the treatment of EOC with HIPEC outside of clinical trial would not be recommended.

References

1. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2018. CA Cancer J. Clin. 2018, 68, 7–30. [CrossRef] [PubMed]

2. Chang, S.J.; Hodeib, M.; Chang, J.; Bristow, R.E. Survival impact of complete cytoreduction to no gross residual disease for advanced-stage ovarian cancer: A meta-analysis. Gynecol. Oncol. 2013, 130, 493–498. [CrossRef] [PubMed]

3. Jayson, G.C.; Kohn, E.C.; Kitchener, H.C.; Ledermann, J.A. Ovarian cancer. Lancet 2014, 384, 1376–1388. [CrossRef]

4. Alberts, D.S.; Liu, P.Y.; Hannigan, E.V.; O'Toole, R.; Williams, S.D.; Young, J.A.; Franklin, E.W. Intraperitoneal cisplatin plus intravenous cyclophosphamide versus intravenous cisplatin plus intravenous cyclophosphamide for stage III ovarian cancer. N. Engl. J. Med. 1996, 335, 1950–1955. [CrossRef] [PubMed]

5. Markman, M.; Bundy, B.N.; Alberts, D.S.; Fowler, J.M.; Clark-Pearson, D.L.; Carson, L.F.; Wadler, S.; Sickel, J. PhaseIII trial of standard-dose in travenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by in travenous paclitaxel and intraperitoneal cisplatinin small-volume stage III ovarian carcinoma: An intergroup study of the Gynecologic Oncology Group, Southwestern Oncology Group, and Eastern Cooperative Oncology Group. J. Clin. Oncol. 2001, 19, 1001–1007. [PubMed]

6. Armstrong, D.K.; Bundy, B.; Wenzel, L.; Huang, H.Q.; Baergen, R.; Lele, S.; Copeland, L.J. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. N. Engl. J. Med. 2006, 354, 34–43. [CrossRef] [PubMed]

7. NCI Clinical Announcement on Intraperitoneal Chemotherapy in Ovarian Cancer. 2006. Available online: https://ctep.cancer.gov/highlights/20060105_ovarian.htm (accesssed on 20 August 2018).

8. Landrum, L.M.; Java, J.; Mathews, C.A.; Lanneau, G.S., Jr.; Copeland, L.J.; Armstrong, D.K.; Walker, J.L. Prognostic factors for stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy: A Gynecologic Oncology Group study. Gynecol. Oncol. 2013, 130, 12–18. [CrossRef] [PubMed]

9. Tewari,D.;Java,J.J.;Salani,R.;Armstrong,D.K.;Markman,M.;Herzog,T.;Monk,B.J.;Chan,J.K.Long-term survival advantage and prognostic factors associated with intraperitoneal chemotherapy treatment in advanced ovarian cancer: A gynecologic oncology group study. J. Clin. Oncol.2015,33,1460–1466. [CrossRef] [PubMed]

10. Walker, J.; Brady, M.F.; DiSilvestro, P.A.; Fujiwara, K.; Alberts, D.; Zheng, W.; Tewari, K.; Cohn, D.E.; Powell, M.; Van Le, L.; et al. A phase III clinical trial of bevacizumab with IV versus IP

chemotherapy in ovarian, fallopian tube, and primary peritoneal carcinoma. NCI-supplied agent: Bevacizumab. NCT01167712, a GOG/NRG trial (GOG 252), in Society of Gynecologic Oncologists. In Proceedings of the 2016 Annual Meeting on Women's Cancer, San Diego, CA, USA, 21 March 2016.

11. Sugarbaker, P.H.; Graves, T.; DeBruijn, E.A.; Cunliffe, W.J.; Mullins, R.E.; Hull, W.E.; Oliff, L.; Schlag, P. Early postoperative intraperitoneal chemotherapy as an adjuvant therapy to surgery for peritoneal carcinomatosis from gastrointestinal cancer: Pharmacological studies. Cancer Res. 1990, 50, 5790–5794. **[**PubMed**]**

12. Katz, M.H.; Barone, R.M. The rationale of perioperative intraperitoneal chemotherapy in the treatment of peritoneal surface malignancies. Surg. Oncol. Clin. N. Am. 2003, 12, 673–688. **[**CrossRef**]**

13. Sun, X.; Li, X.F.; Russell, J.; Xing, L.; Urano, M.; Li, G.C.; Humm, J.L.; Ling, C.C. Changes in tumor hypoxia induced by mild temperature hyperthermia as assessed by dual-tracer immunohistochemistry. Radiother. Oncol. 2008, 88, 269–276. **[**CrossRef**] [**PubMed**]**

14. Petrillo,M.;DeIaco,P.;Cianci,S.;Perrone,M.;Costantini,B.;Ronsini,C.;Scambia,G.;Fagotti,A.Long-Term Survival for Platinum-Sensitive Recurrent Ovarian Cancer Patients Treated with Secondary Cytoreductive Surgery Plus Hyperthermic Intraperitoneal Chemotherapy (HIPEC). Ann. Surg. Oncol. 2016, 23, 1660–1665. **[**CrossRef**] [**PubMed**]**

15. Teicher, B.A.; Kowal, C.D.; Kennedy, K.A.; Sartorelli, A.C. Enhancement by hyperthermia of the in vitro cytotoxicity of mitomycin C toward hypoxic tumor cells. Cancer Res. 1981, 41, 1096–1099. **[**PubMed**]**

16. El-Kareh, A.W.; Secomb, T.W. A theoretical model for intraperitoneal delivery of cisplatin and the effect of hyperthermia on drug penetration distance. Neoplasia 2004, 6, 117–1127. **[**CrossRef**] [**PubMed**]**

17. VanderWaal, R.; Thampy, G.; Wright, W.D.; Roti Roti, J.L. Heat-induced modifications in the association of specific proteins with the nuclear matrix. Radiat. Res. 1996, 145, 746–753. **[**CrossRef**] [**PubMed**]**

18. Roti Roti, J.L.; Kampinga, H.H.; Malyapa, R.S.; Wright, W.D.; vanderWaal, R.P.; Xu, M. Nuclear matrix as a target for hyperthermic killing of cancer cells. Cell Stress Chaperones 1998, 3, 245–255. **[**CrossRef**]** Cancers 2018, 10, 296 9 of 10

19.Chua,T.C.;Yan,T.D.;Saxena,A.;Morris,D.L.Shouldthetreatmentofperitonealcarcinomatosisbycytoreductive surgery and hyperthermic intraperitoneal chemotherapy still be regarded as a highly morbid procedure? A systematic review of morbidity and mortality. Ann. Surg.2009,249,900–907. [CrossRef][PubMed]

20. Voron, T.; Eveno, C.; Jouvin, I.; Beaugerie, A.; Lo Dico, R.; Dagois, S.; Soyer, P.; Pocard, M. Cytoreductive surgery with a hyperthermic intraperitoneal chemotherapy program: Safe after 40 cases, but only controlled after 140 cases. Eur. J. Surg. Oncol. 2015, 41, 1671–1677. [CrossRef] [PubMed]

21. Jafari, M.D.; Halabi, W.J.; Stamos, M.J.; Nguyen, V.Q.; Carmichael, J.C.; Mills, S.D.; Pigazzi, A. Surgical outcomes of hyperthermic intraperitoneal chemotherapy: Analysis of the american college of surgeons national surgical quality improvement program. JAMA Surg. 2014, 149, 170–175. [CrossRef] [PubMed]

22. 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;136:130-135.

23. Van Driel, W.J.; Koole, S.N.; Sonke, G.S. Hyperthermic Intraperitoneal Chemotherapy in Ovarian Cancer. N. Engl. J. Med. 2018, 378, 1363–1364. [CrossRef] [PubMed]

24. Vergote, I.; Trope, C.; Amant, F.; Kristensen, G.; Ehlen, T.; Johnson, N.; Verheijen, R.; van der Burg, M.; Lacave, A.; Benedettie Panici, P.; et al. Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N. Engl. J. Med. 2010, 363, 943–953. [CrossRef] [PubMed]

25. Kireeva, G.S.; Gafton, G.I.; Guseynov, K.D.; Senchik, K.Y.; Belyaeva, O.A.; Bespalov, V.G.; Panchenko, A.V.; Maydin, M.A.; Belyaev, A.M. HIPEC in patients with primary advanced ovarian cancer: Is there a role? A systematic review of short- and long-term outcomes. Surg. Oncol. 2018, 27, 251–258. [CrossRef] [PubMed]

26. Di Giorgio, A.; De Iaco, P.; De Simone, M.; Garofalo, A.; Scambia, G.; Pinna, A.D.; Verdecchia, G.M. Cytoreduction (Peritonectomy Procedures) Combined with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in Advanced Ovarian Cancer: Retrospective Italian Multicenter Observational Study of 511 Cases. Ann. Surg. Oncol. 2017, 24, 914–922. [CrossRef] [PubMed]

27. Bakrin, N.; Bereder, J.M.; Decullier, E.; Classe, J.M.; Msika, S.; Lorimier, G.; Abboud, K. Peritoneal carcinomatosis treated with cytoreductive surgeryand Hyperthermic Intraperitoneal

Chemotherapy(HIPEC) for advanced ovarian carcinoma: A French multicentre retrospective cohort study of 566 patients. Eur. J. Surg. Oncol. 2013, 39, 1435–1443. [CrossRef] [PubMed]

28. Zivanovic, O.; Abramian, A.; Kullmann, M.; Fuhrmann, C.; Coch, C.; Hoeller, T.; Ruehs, H. HIPEC ROC I: A phase I study of cisplatin administered as hyperthermic intraoperative intraperitoneal chemoperfusion followed by postoperative intravenous platinum-based chemotherapy in patients with platinum-sensitive recurrent epithelial ovarian cancer. Int. J. Cancer 2015, 136, 699–708. [CrossRef] [PubMed]

29. Spiliotis, J.; Halkia, E.; Lianos, E.; Kalantzi, N.; Grivas, A.; Efstathiou, E.; Giassas, S. Cytoreductive surgery and HIPEC in recurrent epithelial ovarian cancer: A prospective randomized phase III study. Ann. Surg. Oncol. 2015, 22, 1570–1575. [CrossRef] [PubMed]

30. Fagotti, A.; Costantini, B.; Petrillo, M.; Vizzielli, G.; Fanfani, F.; Margariti, P.A.; Turco, L.C.; Piovano, E.; Scambia, G. Cytoreductive surgery plus HIPEC in platinum-sensitive recurrent ovarian cancer patients: A case-control study on survival in patients with two year follow-up. Gynecol. Oncol. 2012, 127, 502–505. [CrossRef] [PubMed]

31. Provencher, D.M.; Gallagher, C.J.; Parulekar, W.R.; Ledermann, J.A.; Armstrong, D.K.; Brundage, M.; Gourley, C.OV21/PETROC: Arandomized Gynecologic Cancer Intergroup phase II study of intraperitoneal versus intravenous chemotherapy following neoadjuvant chemotherapy and optimal debulking surgery in epithelial ovarian cancer. Ann. Oncol. 2018, 29, 431–438. [CrossRef] [PubMed]