Is minimal invasive surgical treatment of ovarian cancer plus HIPEC a utopia? A review of the literature

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The purpose of this study is to evaluate the effectiveness and safety of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) approached by minimally invasive surgical (MIS) techniques. We conducted a systematic review of the published relevant studies and evaluated a total of 403 patients, with a median age of 57 years old (20–69). The histology of the patients included 160 (39.7%) patients with pseudomyxoma peritonei, 43 (10.6%) with mesothelioma peritonei, 37 (9.2%) with epithelial ovarian cancer (EOC), 80 (19.8%) with appendiceal cancer and 26 (6.4%) with colon cancer, while the histology of the rest of the patients was not specified in the studies. The median Peritoneal Cancer Index (PCI) was 4 (1–10) and complete cytoreduction (CRS) in combination with HIPEC was achieved in 239 patients (60%). 145 (36%) of the patients underwent omentectomy, 37 patients (9.2%) underwent ileocecal resection, 41 patients (10.1%) underwent salpingo-oophorectomy, 6 (1.5%) small bowel resection, 28 (6.7%) peritonec- tomy. Additionally, CRS is characterised by high complexity and demands advanced technical skills, multiple different procedures in order to achieve R0 resection. As a result, various technical limitations apply regarding the implementation of a minimally invasive approach in CRS and HIPEC surgery.

However, MIS techniques have been gaining popularity among gynecologists, ensuring advantages such as lower morbidity, shorter hospital stay and minimised postoperative complications compared to laparotomy. Furthermore, the amplification of the surgical field that is achieved in combination with the updated technological equipment that is used provides an enhanced observation of the entire peritoneal cavity, which constitutes the major prognostic factor of a successful CRS.

Minimally invasive HIPEC has been presented in some studies describing the approach in the treatment of a number of low grade PMP and MP or as an effort to control refractory ascites in a palliative setting. However, the aim of our study is to evaluate the feasibility of the combination of minimally invasive HIPEC and CRS in highly selected patients with peritoneal carcinomatosis.

2. Materials and methods

2.1 Data sources

A meticulous search of the literature was performed up to April 2021 by two independent authors (VP, AF) using the key words: (HIPEC) and (minimal invasive surgery) as search terms. The inclusion criteria were clearly specified and no discrepancies in the results were reported.

2.2 Study selection criteria

All studies presenting a minimally invasive approach of Hyperthermic Intraperitoneal Chemotherapy (HIPEC) were included in our review. Animal studies, manuscripts presented in scientific conferences or studies written in languages other than English, German and Greek were excluded.
2.3 Selected studies

We retrieved a total of 17 studies. 6 articles were considered to be eligible for inclusion in our review, while 11 were excluded since they did not refer to a MIS procedure. 10 studies were excluded after detailed screening according to specific criteria (reviews, letters, editorials, conference papers) and one study in Romanian was excluded. Additionally, through hand search another 10 studies were included in our review. Three studies describing the combination of MIS techniques and CRS + HIPEC were found, but they referred to palliative treatment of malignant ascites. Finally, another study found through hand search referred to minimally invasive application of HIPEC, but without CRS and it was excluded from our study (Fig. 1).

3. Results

In Table 1 the data collected from studies presenting cases of minimally invasive CRS and HIPEC are summarised.

In total 403 patients were evaluated. The median age of the patients was 57 years old (20–69). 14 of the patients were men and 20 were women, while the gender of 8 patients was not specified in the studies. The median Peritoneal Cancer Index (PCI) was 4 (1–10) and the mean operative time was 240 min (90–510). The surgical procedures that were performed included omentectomy in 145 of the patients (36%), cecum/right colectomy in 37 patients (9.2%), salpingovariectomy in 41 patients (10.1%), small bowel resection in 6 (1.5%), peritonectomies in 28 (6.7%), sigmoidectomy in 9 (2.2%), appendectomy in 107 (26.5%), when none of the patients underwent an ileostomy. In 239 patients (60%) complete cytoreduction (R0) was achieved. In total, 13 (3.2%) of the procedures were converted to laparotomy, while in 32 (7.9%) an intestinal anastomosis or suture was required. The median length of stay was 4.5 days (3–6) and the median follow-up of the patients was 13.5 months (1–72).

Finally, regarding the histology, 160 (39.7%) of the patients were treated for pseudomyxoma peritonei, 43 (10.6%) for mesothelioma peritonei, 37 (9.2%) for epithelial ovarian cancer (EOC), 80 (19.8%) for appendiceal cancer and 26 (6.4%) for colon cancer, while the histology of the rest of the patients was not specified in the studies.

4. Discussion

The present study presented the currently available data in the literature regarding the minimally invasive Hyperthermic Intraperitoneal Chemotherapy (HIPEC). According to our findings, minimal invasive HIPEC was associated with acceptable oncological outcomes with a complete cytoreduction rate of about 50% as well as short operative times and hospital stay, low prevalence of intraoperative conversion and postoperative complications.

Esquivel et al. [8] were the first to report in 2009 a case of a successfully completed combined laparoscopic CRS and HIPEC procedure in a patient with peritoneal mesothelioma. Later in 2014, Passot et al. [9] conducted compared patients with both multicystic mesothelioma (MM) and low-grade
scopic procedure. Single-port approach is in more detail pre-
etectomy, peritonectomy and HIPEC via a single port laparo-
patient with a low-grade appendiceal mucinous neoplasm suc-
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report by Alshammari
nestingly, similar encouraging results are presented in a case
after a median follow-up of 11 months were reported. Inter-
tions, postoperative morbidities and oncological outcomes
hospitalization and similar operative times, visceral resec-
procedure was accompanied with complete cytoreduc-
ating from pseudomyxoma peritonei or colorectal cancer.
alar operative times but much shorter median hospital stay,
first group, without any conversion to laparotomy, with sim-

tive in this group of patients. In that setting, the retrospec-
chemotherapy, the Peritoneal Recirculation System (PRS-1.0
the cases, parallely augmenting the survival rate of the pa-
From the classic laparoscopy, variations of the technique
also underwent laparoscopic CRS and HIPEC with a his-
tique via laparotomy. R0 was achieved in all patients in the
without any conversion to laparotomy, with sim-
ular operative times but much shorter median hospital stay,
with the author suggesting the safety and efficacy of the la-

Apart from the classic laparoscopy, variations of the tech-
MIS approach is efficient in highly selected patients with peritoneal surface, specifically interpreted as a PCI of 10 or less [3].

Furthermore, in the study of Arjona-Sanchez including 8 patients with a wider variety of malignancies including ex-
cept for primary peritoneal tumours, advanced carcinomas of the ovaries and the colon accompanied by peritoneal metas-
tasis, the authors concluded that a MIS approach is efficient in highly selected patients with peritoneal surface, specifically interpreted as a PCI of 10 or less [3].

Regarding advanced peritoneal cancer patients, it is worth mentioning that promising results have been presented by
studies evaluating the laparoscopic application of HIPEC in patients with malignant ascites resulting from peritoneal car-
cinomatosis. Facchiano et al. [5] used this technique in treating 5 patients with malignant ascites secondary to un-
resectable peritoneal carcinomatosis of gastric origin and re-
ported complete clinical regression in all of the cases. Simi-
larly, Patriti et al. [6] successfully treated a patient with ma-
lignant ascites resulting from peritoneal mesothelioma by la-
paroscopic HIPEC too. In 2012 Valle et al. [7], applied laparo-
scopically HIPEC to 33 patients with malignant ascites and
unresectable peritoneal carcinomatosis from gastric, colon
and breast cancer as well as patients with mesothelioma and
complete disappearance of the ascites was observed in all of
the cases, parallely augmenting the survival rate of the pa-
tients as well as their quality of life. Moreover, Badgwell et al.
[12] laparoscopically applied HIPEC without CRS in 19 pa-
tients with gastric carcinoma and positive peritoneal cytology
or peritoneal carcinomatosis after systemic chemotherapy,
while Cianci et al. [13] evaluated the application of a new device using CO2 technology for loco-regional intraperitoneal
chemotherapy, the Peritoneal Recirculation System (PRS-1.0
Combat) with very promising results, suggesting that there
is a role of MIS HIPEC not only curative but also pallia-
tive in this group of patients. In that setting, the retrospec-
tive evaluation of minimally invasive secondary cytoreduc-
tion and HIPEC by Fagotti et al. [14] requires further inves-
tigation regarding the research on Minimal Invasive Surgery-
Interval Debulking Surgery (MIS IDS) and HIPEC and large
trials are needed to indicate any possible role. The LANCE
(Laparoscopic cytoreduction After Neoadjuvant ChEmother-
apy) trial seeks to answer these questions, hypothesizing that
for patients who responded to neoadjuvant chemotherapy,
imminently invasive interval debulking surgery and laparo-
tomy are equally effective [15]. After all, a systematic re-

### Table 1. Main characteristics and outcomes of the patients undergoing minimal invasive HIPEC.

| Demographics | n/N (%) |
|-------------|--------|
| Age (median, range) | 57 years (20–69) |
| Peritoneal Cancer Index (median, range) | 4 (1–10) |
| Surgical procedures |
| Omentectomy | 145/403 (36%) |
| Cecum/Right colectomy | 37/403 (9.2%) |
| Salpingovariectomy | 41/403 (10.1%) |
| Small bowel resection | 6/403 (1.5%) |
| Peritonectomies | 28/403 (6.7%) |
| Sigmoidectomy | 9/403 (2.2%) |
| Appendectomy | 107/403 (26.5%) |
| Ileostomy | 0 (0%) |
| OP-time (min) (median, range) | 240 (90–510) |
| complete CR (R0) | 239/403 (60%) |
| Conversion to open | 13/403 (3.2%) |
| Intestine anastomosis or suture | 52/403 (7.9%) |
| Length of stay (median, range) | 4.5 days (3–6) |
| Histology |
| Pseudomyxoma peritonei (PMP) | 160/403 (39.7%) |
| Mesothelioma peritonei (MP) | 43/403 (10.6%) |
| Epithelial Ovarian Cancer (EOC) | 37/403 (9.2%) |
| Appendiceal | 80/403 (19.8%) |
| Colon | 26/403 (6.4%) |
| Follow up (median, range) | 13.5 months (1–72) |

n, number of specific cases; N, total number of patients.

pseudomyxoma peritonei (PMP) and limited peritoneal dis-
ease who underwent laparoscopic CRS and HIPEC with a his-
torical cohort of similar patients treated with the same tech-
nique via laparotomy. R0 was achieved in all patients in the
first group, without any conversion to laparotomy, with sim-
ular operative times but much shorter median hospital stay,
with the author suggesting the safety and efficacy of the la-
paroscopic combination of CRS and HIPEC.

More specifically, Salti et al. [10] described the application of hand-assisted laparo-
soscopic cytoreductive surgery and hyperthermic intraperi-
toneal chemotherapy for peritoneal surface malignancy origin-
ating from pseudomyxoma peritonei or colorectal cancer.
The procedure was accompanied with complete cytoreduc-
tion in all 11 cases while significantly less blood loss, shorter
hospitalization and similar operative times, visceral resec-
tions, postoperative morbidities and oncological outcomes
after a median follow-up of 11 months were reported. Inter-

tently, similar encouraging results are presented in a case
report by Alshammari et al. [2], where for the first time a pa-
tient with a low-grade appendiceal mucinous neoplasm suc-


tively underwent CRS including partial cecectomy, omen-
tectomy, peritoneectomy and HIPEC via a single port laparo-
scopic procedure. Single-port approach is in more detail pre-
view by Gueli Alletti et al. [16] demonstrated the efficacy and safety of MIS techniques regarding the treatment of advanced ovarian cancer patients and more interestingly the same team suggested that the application of MIS techniques in that very sensitive group of patients plays also a very important role in their psycho-oncologic effect and their quality of life [17]. Furthermore, the INTERNATIONAL MIS-ION study by Fagotti et al. [18] as well as a retrospective cohort study by Gallotta et al. [19] recently demonstrated that MIS-interval debulking surgery (IDS) can also be an alternative treatment for ovarian cancer patients undergoing secondary cytoreduction following neoadjuvant chemotherapy (NACT). In that setting, a recent review by Uccela et al. [20] further suggested that minimal invasive techniques are also eligible for treating selected patients with ovarian cancer recurrence. Interestingly, specifically for ovarian cancer, HIPEC for Ovarian Cancer OVHIPEC phase 3 randomized trial has already shown that the addition of HIPEC to interval CRS for patients not eligible for primary debulking surgery, significantly augmented the recurrence-free and overall survival, with similar intraoperative and postoperative complications [21]. The aforementioned trials’ outcomes will be of great interest in combination with the findings of OVHIPEC-2, another phase 3 randomized trial that started in January 2020 and on positive findings will confirm the improvement of overall survival in ovarian cancer patients undergoing primary debulking surgery with the addition of HIPEC [22].

Last but not least, further research is warranted with regards to the pharmacokinetic mechanisms that define the absorption of the pharmaceutical regiment applied during HIPEC procedures. Already in 2008, Gesson-Paute et al. [23] indicated the enhanced tissue uptake of oxaliplatin hat was observed in an animal study comparing the pharmacokinetics between open surgery and laparoscopy in pigs. Similar results are confirmed by Petrillo et al. [24] in a prospective human study where a higher peritoneal absorption of cisplatin is reported in the minimal invasive arm when compared to the open surgery [25].

To our knowledge, the present study is the first presenting a report of the outcomes of patients undergoing CRS and HIPEC via a minimally invasive technique. However, several limitations need to be taken under consideration. First of all, the number of the studies included is limited and as a result so is the number of the patients enrolled. Furthermore, in many of them, specific parameters that we evaluate like the PCI, the R0 resection rate, as well as the type of surgery, the length of stay or the follow-up period are not reported. Secondly, most of the studies included are retrospective or pilot studies or cases reports. Further, random control trials are warranted in order to draw safe conclusions.

5. Conclusions

Minimal invasive cytoreduction surgery and HIPEC are feasible and can be considered as an alternative approach for patients with primary or secondary peritoneal carcinomatosis. Larger meta-analyses including multicenter randomized control trials are necessary to specify the exact profile of the patients that could benefit from this treatment strategy.

Author contributions

VP collected, managed and analyzed the data, consulted the manuscript. AF and AP collected the data, managed and wrote the manuscript. CI developed the protocol/project, managed the data and consulted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. AF, VP, AP and CI are the Guest Editors of this journal, given their roles as Guest Editors, had no involvement in the peer-review of this article and had no access to information regarding its peer-review.

References

[1] Dumont F, Duchalais E, Aumont A, Thibaudeau E. Cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy by laparoscopy via a single-port approach for low-grade peritoneal malignancy. Surgical Endoscopy. 2020; 34: 2789–2795.
[2] Alshammary T, Alshammary S, Hakami R, Alharbi A, Alyami M, Abdulla M, et al. Single-port laparoscopic cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. American Journal of Case Reports. 2019; 20: 1648–1651.
[3] Acevedo-Sanchez A, Ruftan-Peña S, Sanchez-Hidalgo JM, Casado-Adam A, Cosano-Alvarez A, Bricetto-Delgado J. Cytoreductive surgery and intraperitoneal hyperthermic chemotherapy (HIPEC) by minimally invasive approach, an initial experience. World Journal of Surgery. 2018; 42: 3120–3124.
[4] Psomiadou V, Prodromidou A, Fotiou A, Lekka S, Iavazzo C. Robotic interval debulking surgery for advanced epithelial ovarian cancer: current challenge or future direction? A systematic review. Journal of Robotic Surgery. 2021; 15: 153–163.
[5] Fachiano E, Scaringi S, Kianmanesh R, Sabate JM, Castel B, Flamant Y, et al. Laparoscopic hyperthermic intraperitoneal chemotherapy (HIPEC) for the treatment of malignant ascites secondary to unresectable peritoneal carcinomatosis from advanced gastric cancer. European Journal of Surgical Oncology. 2008; 34: 154–158.
[6] Patriti A, Cavazzoni E, Graziosi L, Pisciaroni A, Luzi D, Gullà N, et al. Successful palliation of malignant ascites from peritoneal mesothelioma by laparoscopic intraperitoneal hyperthermic chemotherapy. Surgical Laparoscopy, Endoscopy & Percutaneous Techniques. 2008; 18: 426–428.
[7] Valle M, Federici O, Garofalo A. Patient selection for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy, and role of laparoscopy in diagnosis, staging, and treatment. Surgical Oncology Clinics of North America. 2012; 21: 515–531.
Esquivel J, Averbach A. Combined laparoscopic cytoreductive surgery and hyperthermic intraperitoneal chemotherapy in a patient with peritoneal mesothelioma. Journal of Laparoendoscopic & Advanced Surgical Techniques. 2009; 19: 505–507.

Passot G, Bakrin N, Isaac S, Decullier E, Gilly FN, Glehen O, et al. Postoperative outcomes of laparoscopic vs open cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy for treatment of peritoneal surface malignancies. European Journal of Surgical Oncology. 2014; 40: 957–962.

Salti GI, Naffouje SA. Feasibility of hand-assisted laparoscopic cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancy. Surg Endoscopy. 2019; 33: 52–57.

Gabriel E, Elii E, Bagaria S, Wasif N, Grotz T, Stauffer J, et al. Robotic-assisted cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (CRS-HIPEC). Journal of Robotic Surgery. 2019; 13: 175–179.

Badgwell B, Blum M, Das P, Estrella J, Wang X, Ho L, et al. Phase II trial of laparoscopic hyperthermic intraperitoneal chemotherapy for peritoneal carcinomatosis or positive peritoneal cytology in patients with gastric adenocarcinoma. Annals of Surgical Oncology. 2017; 24: 3338–3344.

Cianci S, Abatini C, Fagotti A, Chiofalo B, Tropea A, Biondi A, et al. Hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal malignancies using new hybrid CO2 system: preliminary experience in referral center. Updates in Surgery. 2019; 71: 555–560.

Fagotti A, Petrillo M, Costantini B, Fanfani F, Gallotta V, Chianteria V, et al. Hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal malignancies using the new CO2 system: a single-institution study. Journal of Gynecologic Oncology. 2014; 132: 303–306.

Nitecki R, Rauh-Hain JA, Melamed A, Scambia G, Pareja R, Coleman RL, et al. Laparoscopic cytoreduction after neoadjuvant chemotherapy (LANCE). International Journal of Gynecologic Cancer. 2020; 30: 1450–1454.

Gueli Alletti S, Capozzi VA, Rosati A, De Blasis I, Cianci S, Vizzielli G, et al. Laparoscopy vs. laparotomy for advanced ovarian cancer: a systematic review of the literature. Minerva Medica. 2019; 110: 341–357.

Gueli Alletti S, Vizzielli G, Lafuenti L, Costantini B, Fagotti A, Fedele C, et al. Single-institution propensity-matched study to evaluate the psychological effect of minimally invasive interval debulking surgery versus standard laparotomic treatment: from body to mind and back. Journal of Minimally Invasive Gynecol. 2018; 25: 816–822.

Fagotti A, Gueli Alletti S, Corrado G, Cola E, Vizza E, Vieira M, et al. The international mission study: minimally invasive surgery in ovarian neoplasms after neoadjuvant chemotherapy. International Journal of Gynecologic Cancer. 2019; 29: 5–9.

Gallotta V, Ghezzi F, Vizza E, Fagotti A, Ceccaroni M, Fanfani F, et al. Laparoscopic management of ovarian cancer patients with localized carcinomatosis and lymph node metastases: results of a retrospective multi-institutional series. Journal of Minimally Invasive Gynecology. 2016; 23: 590–596.

Uccella S, Franchi MP, Cianci S, Zorzato PC, Bertoli F, Alletti SG, et al. Laparotomy vs. minimally invasive surgery for ovarian cancer recurrence: a systematic review. Gland Surgery. 2020; 9: 1130–1139.

Koole SN, Brujs L, Fabris C, Sikorska K, Engbersen M, Schagen van Leeuwen JH, et al. Central radiology assessment of the randomized phase III open-label OVIHPEC-1 trial in ovarian cancer. International Journal of Gynecologic Cancer. 2020; 30: 1928–1934.

Koole S, van Stein R, Sikorska K, Barton D, Perrin L, Brennan D, et al. Primary cytoreductive surgery with or without hyperthermic intraperitoneal chemotherapy (HIPEC) for epithelial ovarian cancer: OVIHPEC-2, a phase III randomized clinical trial. International Journal of Gynecologic Cancer. 2020; 30: 888–892.

Gesson-Paute A, Ferron G, Thomas F, de Lara EC, Chatelut E, Querleu D. Pharmacokinetics of oxaliplatin during open versus laparoscopically assisted heated intraoperative intraperitoneal chemotherapy (HIPEC): an experimental study. Annals of Surgical Oncology. 2008; 15: 339–344.

Petrillo M, Zucchetti M, Cianci S, Morosi L, Ronsini C, Colombo A, et al. Pharmacokinetics of cisplatin during open and minimally-invasive secondary cytoreductive surgery plus HIPEC in women with platinum-sensitive recurrent ovarian cancer: a prospective study. Journal of Gynecologic Oncology. 2019; 30: e59.

Bălescu I, Godoroja D, Gongu M, Tomulescu V, Copăescu C. Laparoscopic HIPEC for peritoneal carcinomatosis from gastric cancer-technique and early outcomes of our first cases. Chirurgia. 2017; 112: 714–725.