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Review

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 Periotoneal Cancer Index (PCI) was 4 (1–10) and complete cytoreduction (R0) was achieved in 239 patients (60%). 145 (36%) of the patients underwent omentectomy, 37 patients (9.2%) underwent cecum/right colectomy, 41 patients (10.1%) underwent salpingovariectomy, 6 (1.5%) small bowel resection, 28 (6.7%) peritonectomies, in 9 (2.2%) sigmoeidectomy and 107 (26.5%) appendectomy, with a mean operative time of 240 min (90–510). Conversion to laparotomywas performed in 13 (3.2%) cases, 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). We concluded that minimal invasive surgery can be considered as an approach in the application of hyperthermic intraperitoneal chemotherapy. Further large studies with higher quality data are warranted to verify our findings.

Keywords

Hyperthermic intraperitoneal chemotherapy; HIPEC; Minimal invasive surgery; MIS; Laparoscopic

1. Introduction

Complete Cytoreductive surgery (CRS) in combination with Hyperthermic Intraperitoneal Chemotherapy (HIPEC) in the optimal treatment option in pseudomyxoma peritonei (PMP) and mesothelioma peritonei (MP) patients, providing very satisfying 5-year overall survival rates (80 to 95%) [1]. Furthermore, the same surgical approach can be applied in the treatment of peritoneal dissemination of low-grade appendiceal mucinous neoplasms [2]. In general, CRS plus HIPEC is one of the treatment options for peritoneal spread of advanced stage malignancies originating from the ovaries, the gastrointestinal system and the peritoneal surface, regardless of the origin of peritoneal metastasis (PM), since drug penetration of systemic chemotherapy into PM is known to be low [3]. The minimal invasive surgical (MIS) approach in such patients has been surrounded by significant debate since historically the standard of care of such patients encompasses access to all four quadrants through an explorative laparotomy. 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 [1].

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 [4].

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 [5–7]. 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.

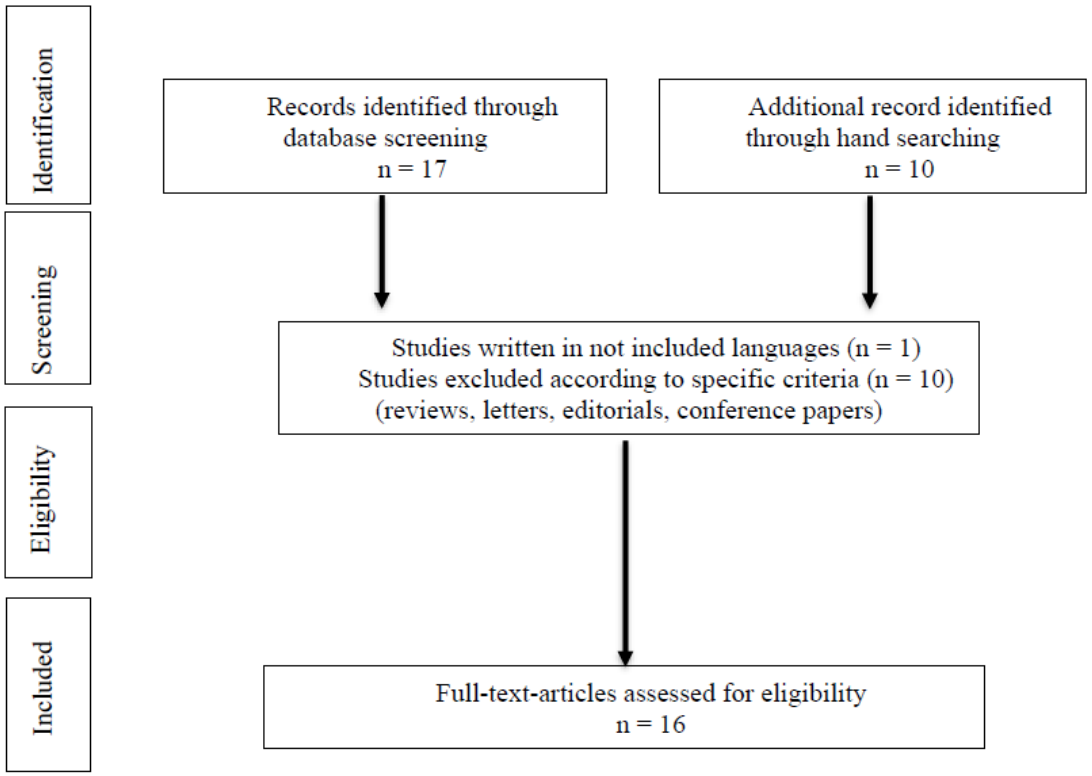

Fig. 1. Systematic review flow diagram.

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 Periotoneal 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%), sigmoeidectomy 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

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%)
Sigmoeidectomy	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	32/403 (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 disease who underwent laparoscopic CRS and HIPEC with a historical cohort of similar patients treated with the same technique via laparotomy. R0 was achieved in all patients in the first group, without any conversion to laparotomy, with similar operative times but much shorter median hospital stay, with the author suggesting the safety and efficacy of the laparoscopic combination of CRS and HIPEC.

Apart from the classic laparoscopy, variations of the technique have been presented. More specifically, Salti *et al.* [10] described the application of hand-assisted laparoscopic cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal surface malignancy originating from pseudomyxoma peritonei or colorectal cancer. The procedure was accompanied with complete cytoreduction in all 11 cases while significantly less blood loss, shorter hospitalization and similar operative times, visceral resections, postoperative morbidities and oncological outcomes after a median follow-up of 11 months were reported. Interestingly, similar encouraging results are presented in a case report by Alshammari *et al.* [2], where for the first time a patient with a low-grade appendiceal mucinous neoplasm successfully underwent CRS including partial cecectomy, omentectomy, peritonectomy and HIPEC via a single port laparoscopic procedure. Single-port approach is in more detail presented in a recent pilot study by Dumont *et al.* [1], where the surgical outcomes of 12 patients with primary peritoneal malignancy treated with this method were presented and operating times as well as the median complication index and the short length of hospital stay confirmed the feasibility of this method to perform CRS and HIPEC, especially in terms of investigation of the small bowel. Interestingly, Gabriel *et al.* [11], reported a case of a patient with a perforated appendiceal mucocele, who was treated with a robot-assisted CRS and HIPEC in a setting of comparable operative times and similar short-term advantages regarding the patient's postoperative course.

Furthermore, in the study of Arjona-Sanchez including 8 patients with a wider variety of malignancies including except for primary peritoneal tumours, advanced carcinomas of the ovaries and the colon accompanied by peritoneal metastasis, 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 carcinomatosis. Facchiano *et al.* [5] used this technique in treating 5 patients with malignant ascites secondary to unresectable peritoneal carcinomatosis of gastric origin and reported complete clinical regression in all of the cases. Similarly, Patriti *et al.* [6] successfully treated a patient with malignant ascites resulting from peritoneal mesothelioma by laparoscopic HIPEC too. In 2012 Valle *et al.* [7], applied laparoscopically 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 patients as well as their quality of life. Moreover, Badgwell *et al.* [12] laparoscopically applied HIPEC without CRS in 19 patients 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 CO_2 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 palliative in this group of patients. In that setting, the retrospective evaluation of minimally invasive secondary cytoreduction and HIPEC by Fagotti *et al.* [14] requires further investigation 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 ChEmotherapy) trial seeks to answer these questions, hypothesizing that for patients who responded to neoadjuvant chemotherapy, minimally invasive interval debulking surgery and laparotomy are equally effective [15]. After all, a systematic re-

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 MISSION 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.

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