JBUON 2021; 26(4): 1669-1678
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Cytoreductive surgery and HIPEC for peritoneal metastasis. Justified hope or desperate illusion? Fifteen years of experience from a Greek Peritoneal Surface Malignancy center

John Spiliotis[1], Nikolaos Kopanakis[2], Alexios Terra[2], Christos Iavazzo[2], Anastasia Prodromidou[2], Athanasios Rogdakis[2], Elias Efstathiou[2]

[1]Department of Surgical Oncology and HIPEC, Athens Medical Centre, Athens, Greece; Department of Surgical Oncology and HIPEC, European Interbalkan Medical Centre, Thessaloniki, Greece. [2]Department of Surgical Oncology, Metaxa Cancer Hospital, Piraeus, Greece

Summary

Purpose: *Peritoneal spread of neoplastic diseases is considered a fatal condition with a dismal prognosis. Few therapeutic options were offered to these patients and surgery had only palliative character. However, advances in surgical techniques and new drugs development, have changed the management of this terminal stage disease. Cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC), has been proposed as a promising alternative to palliative surgery and systemic chemotherapy, since 1980s. Many changes through all these years have refined the technique and standardized indications and limits.*

Methods: *A retrospective study was performed in our medical records, of all patients treated with CRS and HIPEC since 2006. Survival, complications and prognostic factors were studied in a total of 632 patients.*

Results: *Female patients were 419 and males were 213. Mean age was 52.6 years. Peritoneal metastases secondary to colorectal cancer were the most frequent treated disease (87 patients), whereas hepatobilliary-pancreatic neoplastic diseases and sarcomas were the less frequent causes of peritoneal carcinomatosis. Patients with peritoneal metastases from ovarian cancer, treated with systemic chemotherapy and then received interval cytoreductive surgery with HIPEC, were the largest group that are still alive (43%), while only 35% of patients with hepatobilliary-pancreatic cancer and peritoneal disease are alive at present. Gender, age, peritoneal cancer index (PCI), completeness of cytoreduction score (CCs), and number of complications were important prognostic factors of overall survival.*

Conclusions: *Peritoneal carcinomatosis is still considered a final stage disease with a poor prognosis. The confinement of the neoplastic disease in the peritoneal cavity has led to the development of local therapies with promising results. CRS and HIPEC have evolved significantly over the past several years and are at the present the most valuable treatment in highly selected patients with peritoneal carcinomatosis.*

Key words: *peritoneal carcinomatosis, ovarian, colorectal, HIPEC*

Introduction

Peritoneal carcinomatosis is the result of dissemination of gastrointestinal or gynecologic malignancies or primary peritoneal neoplasms in the peritoneal cavity. It has been always considered a final stage disease, and treatment of these patients was a challenging medical action. The conventional approach for many decades was palliative chemotherapy with surgery reserved only for complications such as intestinal obstruction [1]. The confinement of the disease in the peritoneal cavity led to the concept of locoregional treatment strategy. Delivering the chemotherapeutic drugs directly in

Corresponding author: Nikolaos Kopanakis, MD, MSc, PhD. Department of Surgical Oncology, Metaxa Cancer Hospital, Botassi 51 street, 18537 Piraeus, Greece.
Tel: +30 6972637555; Email: nikopanakis@gmail.com
Received: 26/02/2021; Accepted: 18/03/2021

the peritoneum, a significantly higher concentration of the selected agent in the locoregional area is achieved, resulting in improved efficacy [2,3].

Since 1930s, extensive operative debulking procedures were described for locally advanced ovarian cancers. Subsequently, intraperitoneal chemotherapy was added to experimental and therapeutic protocols, for the treatment of peritoneal carcinomatosis from ovarian or other gastrointestinal cancers. Hyperthermia was later added to intraperitoneal chemotherapy, in order to increase the efficacy and peritoneal penetration of the chemotherapeutic drugs [4].

Peritonectomy procedures have been described by Sugarbaker [5], back in 1995, being part of cytoreductive surgery (CRS). Furthermore, visceral resections are often required in order to eliminate all macroscopic disease more than 2.5 mm. It has been proved that this is the single most important prognostic factor [2]. Small peritoneal tumor implants, <2.5 mm, are more sensitive to intraperitoneal chemotherapy, that can be delivered in high doses, without the complications of systemic chemotherapy.

The intraperitoneal delivery of the chemotherapeutic drugs achieves higher concentration of the selected chemotherapeutic agent in the peritoneal cavity, resulting in improved efficacy [2,3]. The peritoneal-plasma barrier is responsible for the limited absorption of the chemotherapeutic agents in the systemic vascular circulation, resulting in less systemic toxicity. Agents used for intraperitoneal chemotherapy must consist of large molecules in order to achieve a prolonged stay in the peritoneal cavity. Local toxicity must be low and should not require metabolization into its active form (usually in the liver). Furthermore, they must be directly cytotoxic, have well-established activity against the malignancy being treated, and demonstrate a pharmacokinetic advantage after intraperitoneal administration [6].

Drugs delivery at a temperature of 39 to 43°C, enhances their antitumoral properties, either by the direct cytotoxic effect of hyperthermia on neoplastic cells or by enhancing drugs pharmacokinetic properties. Malignant cells are selectively destroyed by hyperthermia in the range of 41 to 43°C. Heat-induced lysosomes are more labile in malignant cells and therefore result in increased destructive capacity [7]. Hyperthermia decreases the microcirculation in most malignant tumours which is in contrast to an increased flow capacity found in normal tissues [8]. This, in combination with depression or complete inhibition of oxidative metabolism in tumour cells subjected to hyperthermia and unaltered anaerobic glycolysis, leads to accumulation of lactic acid and lower pH in the microenvironment of the malignant cell. This results in accelerated cell death of the more fragile malignant cells subjected to hyperthermia [9] as compared to normal cells.

Several agents have been shown to have an apparently improved therapeutic index and efficacy when used with hyperthermia. The highest thermal enhancement ratios have been observed for alkylating agents [10].

The most popular methods of HIPEC delivery, are the open approach or "Coliseum" technique and the closed technique. The main benefit of the Coliseum technique is that heated chemotherapy is adequately distributed throughout the abdominal cavity and there is no pooling of temperature or chemotherapy. On the other hand, heat dissipation due to the open abdomen, makes it more difficult to initially achieve a hyperthermic state. Another possible disadvantage is the increased exposure of operating room personnel to chemotherapy. Stuart et al [11] evaluated the safety of operating room personnel during the Coliseum technique and concluded that there is no risk of contamination from the chemotherapeutic drugs.

The closed technique is preceded by the closure of the abdominal wall prior to infusion of the chemotherapeutic drugs. Abdominal wall closure provides a space in which flow rates can be maintained for homogeneous hyperthermia and exposure as well as instillation of positive pressure to enhance drug penetration [12]. The major disadvantage of the closed technique is the uneven distribution of chemotherapeutic agents within the peritoneal cavity, leading to pooling of fluids and accumulation of toxic concentrations of agents and heat [13].

Peritoneal carcinomatosis index (PCI) is a tool to evaluate the preoperative and intraoperative extent of the disease. The peritoneal cavity is divided in 13 regions and a score from 1 to 3, depending on the lesion size, is recorded for each one. A final score from 1 to 39 can be used as a prognostic indicator for the disease course [14]. The degree of cytoreduction (CRS) has also been recognized as an important operative factor associated with prognosis. The completeness of cytoreduction (CC) evaluates the largest residual tumor nodules. Patients with no visible residual tumor after surgical debulking are given a score of CC-0, while those with largest residual tumor nodules <2.5 mm are given CC-1 scores. CC-2 is designated for largest tumor deposits between 2.5 mm and 2.5 cm in size and CC-3 is for tumors greater than 2.5 cm or confluence of multiple smaller nodules. Ideally, surgery with therapeutic intent is aimed at achieving CC of 1 or less [4].

Cytoreductive surgery and HIPEC have evolved significantly over the past several years and many randomized trials have already confirmed the efficacy and the limits of the technique. Patient selection is of great importance in order to individualize the suitable candidates who will benefit from this treatment.

Methods

A retrospective analysis of our data was performed. The research was conducted on patient's medical record and a meticulous follow up. From 2006 to 2019 a total of 632 patients (419 women and 213 men) were treated for peritoneal carcinomatosis (Figure 1). Their median age was 52 years.

Ovarian cancer was the most frequent cause of peritoneal carcinomatosis in our series while sarcomas and hepatobiliary-pancreatic cancer were responsible only for a small number of cases (Figure 2)

Patients with ovarian cancer were divided in 3 distinctive groups in relation to the treatment strategy. In the first group (Upfront), patients were treated with primary cytoreductive surgery (CRS) and HIPEC. The second group (Intervall) included patients that have been treated initially with 3 cycles of chemotherapy with carboplatin and paclitaxel, and then offered CRS and HIPEC. Finally the third group consisted of patients that presented with recurrent peritoneal disease, during follow up, and treated with CRS and HIPEC.

Patients with colorectal cancer were also divided in two groups. The first group consisted of patients that were diagnosed with synchronous peritoneal disease and colorectal cancer (SCPM) and the second group presented metachronous peritoneal disease during follow up (MCPM) (Table 1).

Statistics

Statistical analyses were performed with SPSS-25. Survival analysis was performed using the Kaplan-Meier method and compared using the Log Rank test. Cox regression analysis served to investigate the variables that influenced total survival time. A p value less than 0.05 was considered statistically significant.

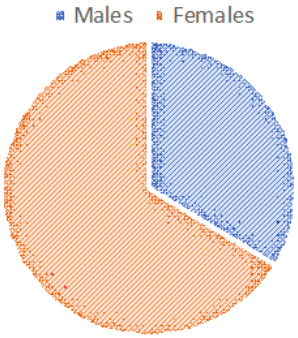

Figure 1. Patient sex.

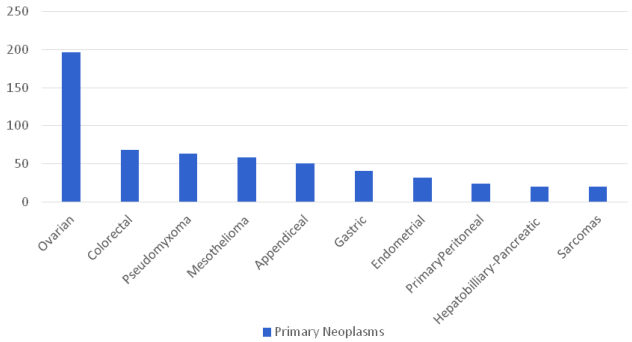

Figure 2. Primary neoplasms.

Table 1. Primary disease distribuition by sex and gender

	Males		*Females*		*Total*	
	n	%	*n*	%	*n*	%
Ovarian cancer (Upfront)	0	0.0	47	11.2	47	7.4
Ovarian cancer (intermediate)	0	0.0	65	15.5	65	10.3
Ovarian cancer (relapse)	0	0.0	85	20.3	85	13.4
Pseudomyxoma peritonei	26	12.2	37	8.8	63	10.0
Appendiceal neoplasms	26	12.2	25	6.0	51	8.1
Mesothelioma	32	15.0	26	6.2	58	9.2
Endometrial cancer	0	0.0	32	7.6	32	5.1
Gastric cancer	24	11.3	17	4.1	41	6.5
Hepatobilliary-Pancreatic cancer	14	6.6	6	1.4	20	3.2
Sarcomas	12	5.6	8	1.9	20	3.2
Primary peritoneal carcinoma	11	5.2	13	3.1	24	3.8
Colorectal cancer (SCPM)	22	10.3	17	4.1	39	6.2
Colorectal cancer (MCPM)	46	21.6	41	9.8	87	13.8

Results

Patients with ovarian cancer that have been treated with primary cytoreductive surgery and HIPEC followed by six cycles of systemic chemotherapy with carboplatin and paclitaxel presented the highest median overall survival of 48 months. Patients with hepatobiliary-pancreatic cancer and peritoneal disease, presented the lowest median overall survival of 18 months (Table 2).

Patients with metachronous colorectal peritoneal metastases, presented a median overall survival of 44 months, distinct from those who presented initially with peritoneal disease, probably reflecting an aggressive tumor biology. Peritoneal carcinomatosis from gastric neoplasms is a debilitating state of disease with a dismal prognosis and a median overall survival of 19 months (Figure 3).

Peritoneal cancer index (PCI) is associated with the ability to achieve a complete cytoreduction and therefore is strictly connected with patient survival. PCI's values less than 10, were correlated with a median overall survival of 40 months, while patients with extended peritoneal disease, presented median overall survival of 12 months, regardless of the primary neoplasm (Table 3, Figure 4).

Completeness of cytoreduction score (CC) is probably the most important predictive factor in terms of survival. Eliminating all visible macro-

Table 2. Median overall survival

Primary neoplasm	*Months*
Ovarian cancer (Upfront)	*48.0*
Ovarian cancer (Interval)	30.0
Ovarian cancer (Reccurence)	30.0
Pseudomyxoma peritonei	34.0
Appendiceal neoplasm	30.0
Mesothelioma	31.0
Endometrial cancer	30.0
Gastric cancer	19.0
Hepatobilliary-Pancreatic cancer	18.0
Sarcomas	26.0
Primaryperitoneal carcinoma	26.0
Colorectal cancer (SCPM)*	44.0
Colorectal cancer (MCPM)**	32.0
Overall	30.0

* SCPM: Synchronous colorectal peritoneal metastases.
**MCPM: Metachronous colorectal peritoneal metastases

Table 3. PCI correlated survival

Peritoneal cancer index (PCI)	*Median survival time (months)*
0-10	40.0
11-20	22.0
>20	12.0
Overall	30.0

Table 4. CC correlated survival

Completeness of cytoreduction score (CCs)	*Median survival time (months)*
CC-0	44.0
CC-1	20.0
CC-2	14.0
CC-3	10.0
Overall	30.0

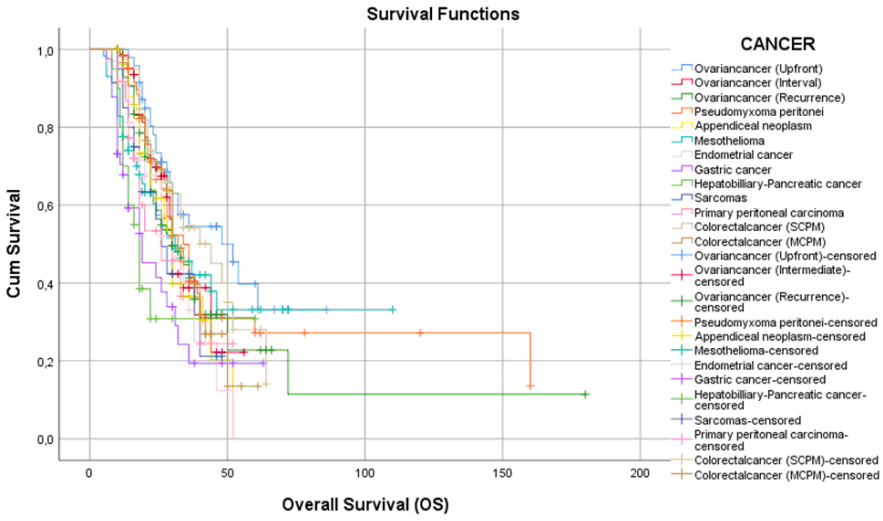

Figure 3. Overall survival.

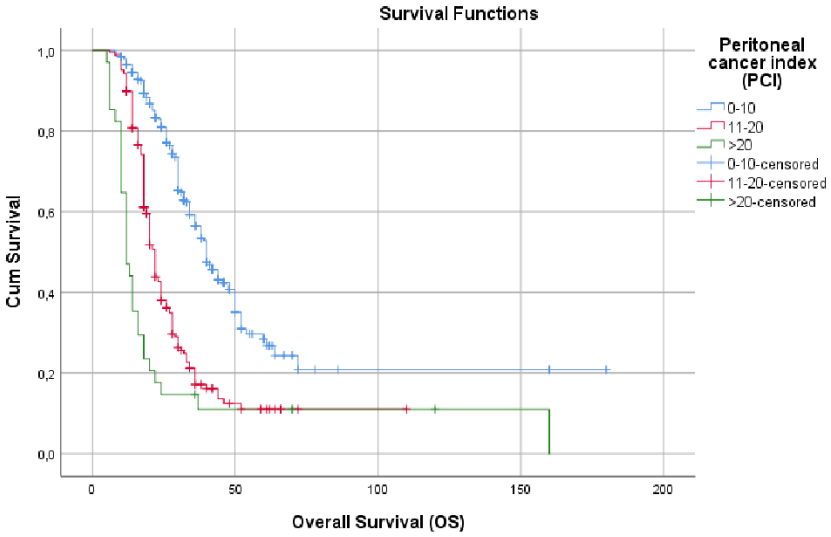

Figure 4. PCI correlated survival.

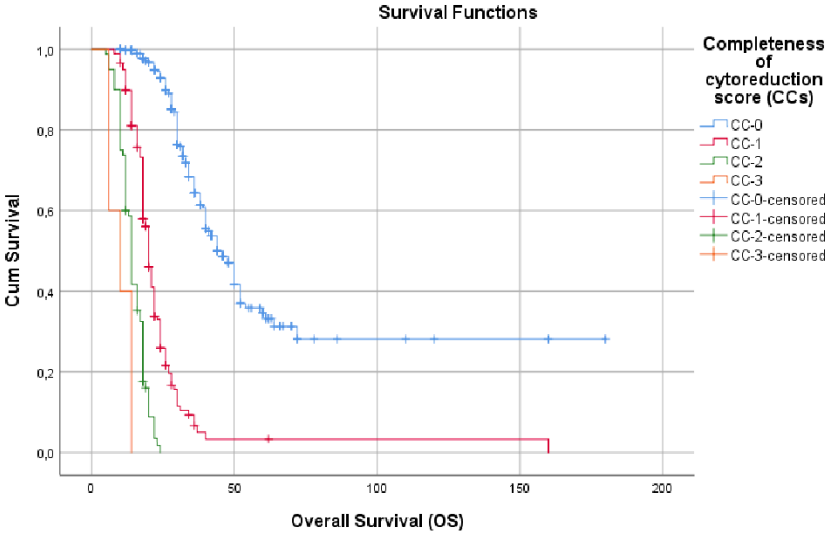

Figure 5. CC correlated survival.

scopic peritoneal disease, permits an optimal penetration of the chemotherapeutic drugs in the peritoneum thereby achieving their maximal cytotoxic effect (Table 4, Figure 5).

Young patients, less than 41 years old, had better chances of long term survival, presenting a median overall survival of 38 months (Table 5, Figure 6)

Using the Cox proportional-hazards model, we investigated the association between the survival time of patients and one or more predictor variables (Table 6).

The risk of death was 22.6% higher in male patients and 38.7% higher in patients that developed at least one complication in comparison with those that were dismissed from the hospital without any complication. Patients with a CC score 1 were 7.3 times in higher risk of dying compared to patients with CC score 0. The same risk was 28.2 and 102 times higher in patients with CC score of 2 and 3, respectively.

Survival function at mean of covariates is presented in Figure 7.

Table 5. Age correlated median survival

Age, years	*Median survival time (months)*
<41	38.0
41-60	30.0
61-70	30.0
>70	26.0
Overall	30.0

Complications grade III-IV according to the Clavien–Dindo classification reached 39%, in the first 90 postoperative days. Respiratory complications were the most frequent (24%), followed by surgical complications (22%). Postoperative fistulas (13%) and bleeding (6%), were the most recorded surgical complications (Figure 8).

A re-operation was required in 10% of the above-mentioned patients. ICU admission was necessary in 22% of the patients with postoperative complications. Mortality was documented at 5% in the first 90 days.

Table 6. Variables in the equation

	B	*SE*	*Wald*	*Df*	*Sig.*	*Exp(B)*
Age	0.004	0.005	0.663	1	0.415	1.004
PCI	-0.016	0.013	1.409	1	0.235	0.984
Gender	0.204	0.114	3.217	1	0.073	1.226
Complications	0.327	0.117	7.854	1	0.005	1.387
CCs			221.964	3	0.000	
CC-1	2.114	0.164	166.533	1	0.000	8.281
CC-2	3.375	0.236	203.812	1	0.000	29.216
CC-3	4.635	0.558	69.006	1	0.000	103.071

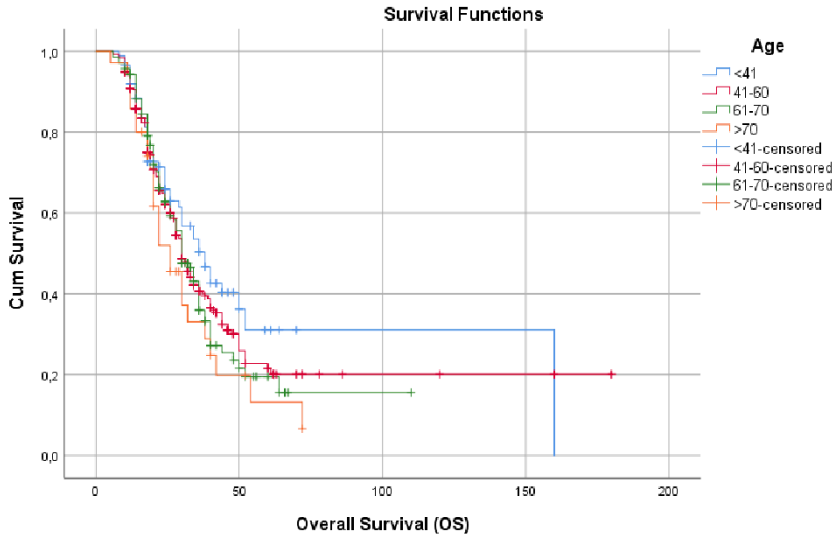

Figure 6. Age correlated median survival.

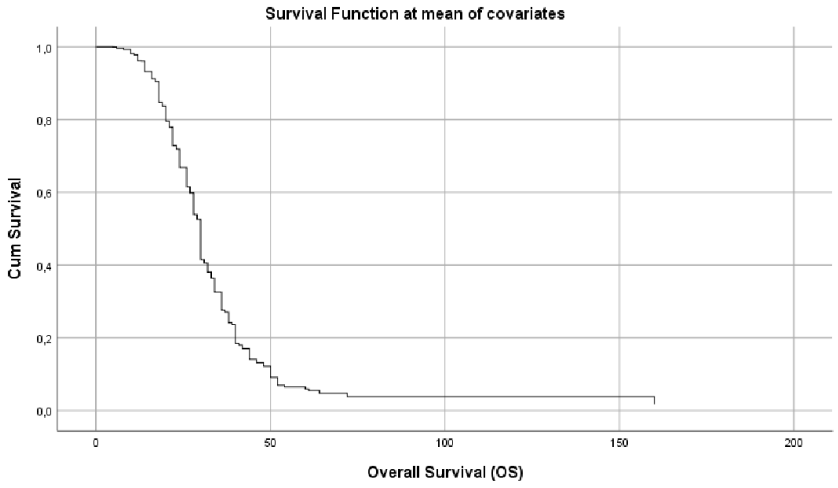

Figure 7. Survival functions covariates.

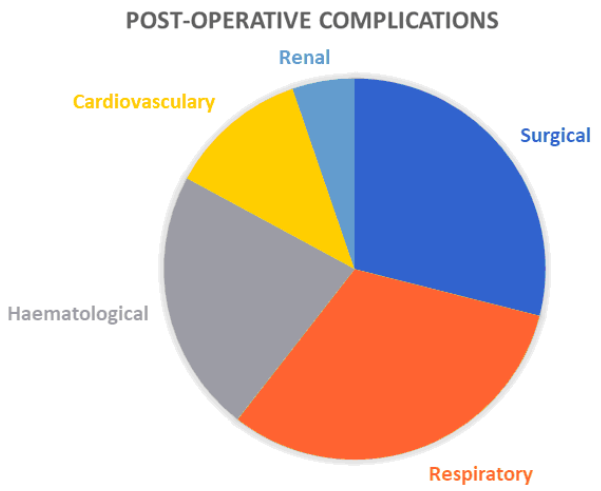

Figure 8. Post-operative complications.

Discussion

Peritoneal metastases may occur from a majority of cancers that occur within the abdomen or pelvis. They have been considered an end-stage disease and palliative systemic chemotherapy was reserved for these patients. Surgery was offered with the intend of treating the complications and attenuate symptoms. In the last 30 years, however, the management of peritoneal carcinomatosis has evolved and survival of patients with peritoneal carcinomatosis has been ameliorated. The concept of locoregional instead of systemic spread of the neoplastic disease has led to more aggressive and extended debulking operations combined with the use of intraperitoneal chemotherapy.

Since 1970, several authors have published the positive correlation between widely debulking operations and survival in female patients with ovarian cancer [15,16]. It seemed that smaller tumor implants were more sensitive to systemic chemotherapy, offering a better therapeutic result in the adjuvant setting. At the same time, authors were studying the efficacy of intraperitoneal delivery of chemotherapeutic drugs demonstrating higher concentrations in the peritoneal cavity after the treatment [17]. Spratt et al was the first to treat a patient with pseudomyxoma peritonei, combining a cytoreductive operation with HIPEC [18]. Later, Sugarbaker at the Washington Cancer Institute, investigated the use of the technique in other gastrointestinal malignancies, reporting the first promising results [19].

The growing interest in the use of CRS and HIPEC, motivated many surgeons in the 90s to get involved with this method and research articles have been published in literature. EVOCAPE I was the first multicentric prospective study to evaluate survival time and prognostic factors in patients with peritoneal carcinomatosis from GI malignancies, treated with HIPEC [20]. The authors concluded that survival rates were mainly affected by the initial spread of the peritoneal disease and that the presence of ascites was associated with poor survival of patients with gastric or pancreatic carcinoma. Differentiation of the primary tumor did not influence the prognosis of patients with PC [20].

However, many retrospective and prospective studies have been published since then, consolidating the role of HIPEC in the treatment of PC from gastrointestinal and gynecologic malignancies.

Cytoreductive surgery and HIPEC are the treatments of choice in patients with pseudomyxoma peritonei (PMP). This rare disease is the result of the rupture of a low-grade mucinous neoplasm of the appendix, resulting in mucinous ascites [21]. Five-year overall survival has been published to range between 23-82% and rates of major complications as high as 24% [22].Several studies have confirmed that aggressive surgical procedures accompanied by HIPEC are associated with an acceptable risk of postoperative complications and mortality [23,24].

Malignant peritoneal mesothelioma (MPM) is a rare malignancy that typically presents with vague symptoms and ascites. It is relatively an uncommon disease with an incidence, in the United States, of 1.94 and 0.41 cases per 100,000 for men and women, respectively [25]. There are no randomized controlled trials in the literature to assess the value of treatment strategies. However, extended surgical resections are still considered the cornerstone of the therapeutic strategies. Many observational studies have confirmed the value of cytoreductive surgery followed by HIPEC [26-28]. Highly selected patients with the epithelioid variant of the disease and a low completeness of cytoreduction score (CCs) are positive prognostic factors for a prolonged OS.

Colon cancer is the third most common cancer worldwide. About 25% of the patients bear metastases at the time of diagnosis and among those cases, up to 8% have synchronous peritoneal carcinomatosis. Metachronous peritoneal metastasis occur approximately in 10% of the patients. Peritoneal metastatic disease is more frequent in colon cancer than in rectal tumors [29].

Those patients were considered only for palliative treatment and surgery was destined for symptoms relief. However, with the evolution of intraperitoneal chemotherapy, the use of HIPEC following an extended cytoreductive surgery has gained wider acceptance [30,31]. Many chemother-

apeutic agents have been used in order to achieve better results. Unpublished data from our group (Spiliotis et al) imply that the use of mitomycin C (MMC) offers a survival advantage over oxaliplatin when used in HIPEC for peritoneal carcinomatosis from colon cancer. Highly selected patients, with limited PCI values, will benefit from the combination of CRS followed by HIPEC and systemic chemotherapy [31]. Randomized controlled trials, and large multicenter cohort studies suggest that possibly a major part of benefit to OS and disease-free survival has to be attributed to cytoreduction [30].

Diffuse peritoneal metastasis, unresectable extra-abdominal disease, extended small bowel serosa or small bowel mesentery involvement and multi-segmentary malignant bowel obstruction are some of the most important exclusion criteria for CRS and HIPEC [32].

A study was recently published by authors who retrospectively reviewed the US HIPEC Collaborative (2000-2017) for patients who underwent CCR0/1 CRS/HIPEC for appendiceal/colorectal cancer. This study correlated the implications of postoperative complications for survival after cytoreductive surgery and HIPEC. The authors concluded that postoperative complications are associated with decreased OS and RFS after CRS/HIPEC for invasive histology, but not for an indolent disease such as non invasive appendiceal neoplasm, and this association was largely driven by infectious complications [33].

Epithelial ovarian cancer (EOC) is the most lethal gynecologic cancer. Most patients, at the moments of diagnosis, present already with advanced disease and peritoneal carcinomatosis that carries a dismal prognosis [34]. Considering the fact that ovarian cancer primarily metastasizes within the peritoneal cavity, intraperitoneal (IP) chemotherapy emerged as a strategy to treat peritoneal disease avoiding the complications of systemic chemotherapy [35]. The initial enthusiasm after the introduction of HIPEC in the treatment of EOC, was followed by skepticism and the role of HIPEC following CRS in the management of primary and recurrent EOC is still controversial [36].

Many authors have published their experience in the upfront treatment of EOC with CRS and HIPEC. The results are non-unanimous and this is probably due to the different strategies used by the authors. The first multicenter phase III randomized controlled trial using HIPEC in the upfront setting in ovarian cancer was published by van Driel et al in 2018 [34]. Patients with stage III ovarian cancer received neoadjuvant systemic chemotherapy with carboplatin or paclitaxel. Those with stable disease after three cycles were randomized at the time of surgery if an optimal cytoreduction was felt to be feasible to either cytoreduction with or without HIPEC using cisplatin 100 mg/m^2. The patients then received three additional cycles of adjuvant IV chemotherapy. The group that received surgery plus HIPEC had a 4-month progression-free survival advantage and a 12-month OS advantage [34]. Lim et al randomized 184 patients with stage III and IV EOC to receive HIPEC or not, after an optimal upfront or interval cytoreduction [37]. The only difference was in the neoadjuvant chemotherapy subgroup that presented a better PFS and OS in those patients that had received CRS and HIPEC. Even if there are still more questions to answer about the right timing of HIPEC in the primary treatment of ovarian cancer, it seems that the best results are achieved at the interval cytoreduction.

OVHIPEC-2 (NCT03772028) has been designed to investigate if HIPEC during upfront cytoreduction is beneficial for these patients. However, it will not be until April 2024, when the estimated primary completion date will be reached when we must wait for the first results [38].

In 2015, we published the results of a randomized controlled trial that we conducted in our hospital, on the use of HIPEC in recurrent ovarian cancer [39]. Patients were randomized into two groups. Those who received secondary CRS+HIPEC and systemic chemotherapy and those who received secondary CRS and systemic chemotherapy alone. Even if our study presented a few weak strategy inaccuracies, we were the first to demonstrate a trend versus a better mean OS in the HIPEC group. We also demonstrated the importance of cytoreduction on OS.

Even if many other retrospective studies were published , focusing on the use of HIPEC in the treatment of recurrent EOC [40-42], prospective multicenter randomized controlled trials are needed to finally confirm the role of the technique in the recurrent disease.

In the 1970s when the first attempts with intraperitoneal chemotherapy were made, a promising hope emerged for the patients with peritoneal carcinomatosis. In the years that followed, cytoreductive surgery and HIPEC have evolved significantly, and became useful weapons in expert hands that were treating patients with peritoneal dissemination of gynecologic or gastrointestinal malignancies.

The initial eagerness was followed by skepticism, when the first results of retrospective studies were published through years demonstrating non-identical conclusions. This was attributed to the different methodology and study design of each

author, but also to the lack of treatment protocols that are slowly emerging the last few years.

Prospective multicenter randomized controlled trials are currently investigating more cancer specific treatments in order to enforce personalized medicine and cover all aspects of HIPEC technique from neo-adjuvant systemic chemotherapy to bidirectional chemotherapy, that consists of administering concomitant IV and intraperitoneal chemotherapy in consecutive sessions [43].

New drugs discovery and evolution of immunotherapy, are offering new fields of research and even more targeted therapies in advanced forms of malignancies that involve the peritoneum. This fact, in addition to a strict patient selection, will transform the hope of winning the battle against peritoneal carcinomatosis to victory against the local spreading of many malignancies in the peritoneal cavity.

Conflict of interests

The authors declare no conflict of interests.

References

1. Sugarbaker PH. Observations concerning cancer spread within the peritoneal cavity and concepts supporting an ordered pathophysiology. Cancer Treat Res 1996;82:79-100.
2. de Bree E, Tsiftsis DD. Principles of perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis. Recent Results Cancer Res 2007;169:39-51.
3. Halkia E, Kopanakis N, Nikolaou G, Spiliotis J. Cytoreductive surgery and HIPEC for peritoneal carcinomatosis. A review on morbidity and mortality. JBUON 2015;20 (Suppl 1):S80-7.
4. Madalyn G Neuwirth, H Richard Alexander, Giorgos C Karakousis. Then and Now: Cytoreductive Surgery With Hyperthermic Intraperitoneal Chemotherapy (HIPEC); a Historical Perspective. J Gastrointest Oncol 2016;7:18-28.
5. Sugarbaker PH. Peritonectomy procedures. Ann Surg 1996;221:29-42.
6. Spiliotis J, Halkia E, de Bree E. Treatment of peritoneal surface malignancies with hyperthermic intraperitoneal chemotherapy-current perspectives. Curr Oncol 2016;23:e266-e275.
7. Sticca RP, Dach BW. Rationale for hyperthermia with intraoperative intraperitoneal chemotherapy agents. Surg Oncol Clin N Am 2003;12:689-701.
8. Dudar TE, Jain RK. Differential response of normal and tumor microcirculation to hyperthermia. Cancer Res 1984;44:605-12.
9. Overgaard J. Effect of hyperthermia on malignant cells invivo. A review and a hypothesis. Cancer 1977;39:2637-46.
10. Takemoto M, Kuroda M, Urano M et al. The effect of various chemotherapeutic agents given with mild hyperthermia on different types of tumours. Int J Hyperthermia 2003;19:193-203.
11. Stuart OA, Stephens AD, Welch L, Sugarbaker PH. Safety monitoring of the coliseum technique for heated intraoperative intraperitoneal chemotherapy with mitomycin C. Ann Surg Oncol 2002;9:186-191.
12. Jacquet P, Stuart OA, Chang D et al. Effects of intraabdominal pressure on pharmacokinetics and tissue distribution of doxorubicin after intraperitoneal administration. Anticancer Drugs 1996;7:596-603.
13. Elias D, Antoun S, Goharin A et al. Research on the bestchemohyperthermia technique of treatment of peritoneal carcinomatosis after complete resection. Int J Surg Investig 2000;1:431-9.
14. Halkia E, Gavriel S, Spiliotis J. Management of peritoneal surface malignancy: a review ofthe recent literature. JBUON 2014;19:618-26.
15. Munnell EW. The changing prognosis and treatment in cancer of the ovary. A report of 235 patients with primary ovarian carcinoma 1952-1961. Am J Obstet Gynecol 1968;100:790-805.
16. Munnell EW. Surgical treatment of ovarian carcinoma. Clin Obstet Gynecol 1969;12:980-92.
17. Pretorius RG, Petrilli ES, Kean CK et al. Comparison of the iv and ip routes of administration of cisplatin in dogs. Cancer Treat Rep 1981;65:1055-62.
18. Spratt JS, Adcock RA, Muskovin M et al. Clinical delivery system for intraperitoneal hyperthermic chemotherapy. Cancer Res 1980;40:256-60.
19. Sugarbaker PH. Surgical management of peritoneal carcinosis: diagnosis, prevention and treatment. Langenbecks Arch Chir 1988;373:189-96.
20. Sadeghi B, Arvieux C, Glehen O et al. Peritoneal carcinomatosis from non-gynecologic malignancies: results of the EVOCAPE 1 multicentric prospective study. Cancer 2000;88:358-63.
21. Mittal R, Chandramohan A, Moran B. Pseudomyxoma peritonei: natural history and treatment. Int J Hyperthermia 2017;33:511-19.
22. Syed Ali Rizvi, Wajahat Syed, Ravi Shergill. Approach to Pseudomyxoma peritonei. World J Gastrointest Surg 2018;10:49-56.
23. Baratti D, Kusamura S, Nonaka D et al. Pseudomyxoma peritonei: clinical pathological and biological prognostic factor in patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (Hipec). Ann Surg Oncol 2008;15:526-534.
24. Vaira M, Cioppa T, de Marco G et al. Management of

Pseudomyxoma Peritonei by cytoreduction+HIPEC (Hyperthermic Intraperitoneal Chemotherapy): Results Analysis of a Twelve-Year Experience. In Vivo 2009;23:639-44.

25. Henley SJ, Larson TC, Wu M et al. Mesothelioma incidence in 50 states and the District of Columbia, United States, 2003-2008. Int J Occup Environ Health 2013;19:1-10.
26. Verma V, Sleightholm RL, Rusthoven CG et al. Malignant peritoneal mesothelioma: national practice patterns, outcomes, and predictors of survival. Ann Surg Oncol 2018;25:2018-26.
27. Yan TD, Welch L, Black D, Sugarbaker PH. A systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for diffuse malignancy peritoneal mesothelioma. Ann Oncol 2007;18:827-34.
28. Levine EA, Stewart J, Shen P, Russell GB, Loggie BL, Votanopoulos KI. Intraperitoneal chemotherapy for peritoneal surface malignancy: experience with 1,000 patients. J Am Coll Surg 2014;218:573-85.
29. Sugarbaker PH. Colorectal cancer: Prevention and management of metastatic disease. Biomed Res Int 2014;2014:782890.
30. Verwaal VJ, Bruin S, Boot H, van Slooten G, van Tinteren H. 8-year follow-up of randomized trial: Cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol 2008;15:2426-32.
31. Elias D, Gilly F, Boutitie F et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: Retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol 2010;28:63-8.
32. Sánchez-Hidalgo JM, Rodríguez-Ortiz L, Arjona-Sánchez A et al. Colorectal peritoneal metastases: Optimal management review. World J Gastroenterol 2019;25:3484-502.
33. Gamboa AC, Lee RM,https://pubmed.ncbi.nlm.nih.gov/?term=Turgeon+MK&cauthor_id=32696303 Turgeon TK et al. Implications of post-operative complications for survival after cytoreductive surgery and HIPEC: A multi-Institutional analysis of the US HIPEC Collaborative. Ann Surg Oncol 2020;27:4980-95.
34. van Driel WJ, Koole SN, Sikorska K et al. Hyperthermic intraperitoneal chemotherapy in ovarian cancer. N Engl J Med 2018;378:230-40.
35. Markman M, Bundy BN, Alberts DS et al. Phase III trial of standard-dose intravenous cisplatin plus paclitaxel versus moderately high-dose carboplatin followed by intravenous paclitaxel and intraperitoneal cisplatin in 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;19:1001-7.
36. Cascales PA, Gil J, Galindo PJ et al. Heterogeneity in patients and methods. A problem for hyperthermic intraoperative intraperitoneal chemotherapy (HIPEC) in ovarian carcinoma. Eur J Obstet Gynecol Reprod Biol 2011;158:361-2.
37. Lim MC, Chang SJ, Yoo HJ, Nam BH, Bristow R, Park SY. Randomized trial of hyperthermic intraperitoneal chemotherapy (HIPEC) in women with primary advanced peritoneal, ovarian, and tubal cancer. J Clin Oncol 2017;35:5520.
38. Koole SN, van Driel WJ, Sonke GS. Hyperthermic intraperitoneal chemotherapy for ovarian cancer: The heat is on. Cancer 2019;125:4587-93.
39. 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.
40. Bakrin N, Cotte E, Golfier F et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) for persistent and recurrent advancedovarian carcinoma: A multicenter, prospective study of 246 patients. Ann Surg Oncol 2012;19:4052-8.
41. Safra T, Grisaru D, Inbar M et al. Cytoreduction surgery with hyperthermic intraperitoneal chemotherapy in recurrent ovarian cancer improves progression-free survival, especially in BRCA-positive patients- a case-control study. J Surg Oncol 2014;110:661-5.
42. Le Brun JF, Campion L, Berton-Rigaud D et al. Survival benefit of hyperthermic intraperitoneal chemotherapy for recurrent ovarian cancer: A multi-institutional case control study. Ann Surg Oncol 2014;21:3621-7.
43. Bijelic L, Stuart OA, Sugarbaker P. Adjuvant bidirectional chemotherapy with intraperitoneal pemetrexed combined with intravenous cisplatin for diffuse malignant peritoneal mesothelioma. Gastroenterol Res Pract 2012. doi:10.1155/2012/890450.