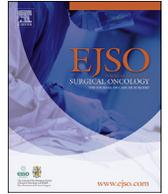


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Current practice of Latin American centers in the treatment of peritoneal diseases with cytoreductive surgery with HIPEC

Latin American Registry of Peritoneal Diseases – LARPD participants¹

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ABSTRACT

Introduction: A combination therapy of cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) has been proposed as a treatment option in patients with peritoneal metastasis of colorectal, ovarian, gastric cancers and sarcomas and as a current standard treatment for pseudomyxoma peritonei and peritoneal mesothelioma. There is a need to standardize its indication, drugs selection along with their concentrations and ways to deliver peritoneal chemotherapy solutions for best outcomes.

Aim of the study: To investigate the current practice of Latin American (LA) Centers in which peritoneal diseases (PD) are treated.

Patient and Methods: All centers from Latin American Registry of Peritoneal Diseases (LARPD) were invited to participate in a two rounds online survey, to describe their current practice in all indications of CRS with HIPEC for PD.

Results: 76 out of 84 LARPD's centers answered the survey, with a response rate of 90,5%. The results represent the current practice of 248 surgeons that are members of LARPD's centers, in 8 LA countries, that at the time of the study had treated 2682 patients with CRS with HIPEC. All current practice aspects including indications, contra-indications, patient selection, methods of peritoneal chemotherapy delivery and treatment protocols are described in this manuscript.

Conclusions: This survey is the first LA effort to publish current practice indications and treatment protocols of PD. Achieving consensus of best therapeutic options is essential to provide the best possible outcomes for patients with PD who could benefit from CRS with HIPEC therefore aiming at standardization of the procedure.

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Introduction

Cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) is the current standard treatment for pseudomyxoma peritonei [1–3] and peritoneal mesothelioma [4,5] and has been considered a therapeutic option for the treatment of selected patients with peritoneal metastasis (PM) of colorectal [6–9], ovarian [10–12], gastric cancers [13] and sarcomas [14]. Despite the most challenging part of the procedure being the CRS, requiring well trained surgeons, there is no doubt regarding its technical aspects, which aims at resecting all organs and peritoneal surface affected by the peritoneal disease (PD) [15–17]. Even though, it is necessary standardization of the indications for CRS with HIPEC, drugs selection along with their concentrations and ways to deliver peritoneal chemotherapy solutions during the HIPEC phase. The indication of who are the best patients to be treated with CRS with HIPEC is also a matter of debate [18]. It is still

Abbreviations: CRS, cytoreductive surgery; HIPEC, hyperthermic intraperitoneal chemotherapy; PD, peritoneal disease; LA, Latin American; LARPD, Latin American Registry of Peritoneal Diseases; PM, peritoneal metastasis; PCI, Peritoneal Cancer Index; ECOG, Eastern Cooperative Oncology Group, performance status criteria; CC0/CC1/CC2/CC3, completeness of cytoreduction score CC. CC0: no visible peritoneal carcinomatosis after CRS. CC-1: nodules persisting <2.5 mm after CRS. CC-2: nodules persisting between 2.5 mm and 2.5 cm. CC-3: nodules persisting >2.5 cm; CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission computed tomography; CEA, carcinoembryonic antigen; CA 125, cancer antigen 125; CA 19.9, carbohydrate antigen 19-9; IP, Intraperitoneal.

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¹ LARPD participants and study contributors are listed in the [Appendix](#) section.

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in discussion if it should be delivered in patients with concomitant resectable hematogenic metastasis and what should be the limit of the peritoneal cancer index (PCI) of patients with colorectal, ovarian, gastric cancers and sarcomas to be submitted to the treatment.

To offer patients the best treatment available, CRS with HIPEC need consensus and protocol standardization [19]. Patients in different countries should be treated according to similar protocols, supported by scientific data. The first step to obtain this goal is investigate how it has been indicated and performed. The present study reveals the current practice of Latin American (LA) centers in which PD is treated.

Material and methods

Inclusion of centers

Centers that perform CRS with HIPEC were identified by searching through network of Brazilian Society of Surgical Oncology, Latin American Society of Surgical Oncology and Peritoneal Surface Oncology Group International and invited to participate of the Latin American Registry of Peritoneal Diseases (LARPD). All centers who informed to perform CRS with HIPEC were included with no restriction. Each center appointed one representative to answer the survey's questionnaires. Every representative was guided to provide information regarding the center's PD treatment protocol and opinion of all of their surgeons in what was being asked, regarding current practice in CRS with HIPEC.

Questionnaire

The survey was divided into two rounds. A web-based survey service (www.surveymonkey.com) was used to construct, distribute and collect the results. The first round questionnaire was designed by the first four authors of this paper, consisted of 108 questions addressing potentially controversial issues and asking the current CRS with HIPEC protocols in the treatment of pseudomyxoma peritonei, peritoneal mesothelioma and PM of colorectal, ovarian, gastric cancers and sarcomas. The 45 representatives from Brazilian centers who perform CRS with HIPEC, enrolled in the study at that time, answered the first round from February 2nd to 28th, 2017.

Questions achieving answers with 75% or more of concordance in this first round were selected by the creators of the survey and incorporated to a second questionnaire with 112 questions, sent to all 84 representatives of the LARPD for the second round of the survey, answered from July 15th to August 21st, 2017.

All data was obtained from questionnaires answered by all co-authors, regarding current medical practice, without any patient information.

Results

Response rate of the first survey questionnaire was 100% (45/45). The second and final survey questionnaire had a response rate of 90,5% (76/84). Table 1 shows the number of centers per countries and the number of cases treated. There were 248 surgeons participating on the 76 centers that answered the two questionnaires, summing up 2682 patients treated with CRS with HIPEC. Regarding the source of payment of the treated patients, 67,1% of the centers indicated having procedures paid by patients private means; 63,2% by health insurance companies and 42,1% by the public health system. A judicial process was required in 52,6% of the centers to have the procedures paid by the government public

Table 1

Number of centers of each Latin American country, informing how many answered the survey questionnaire and number of patients with peritoneal diseases treated.

Countries	Centers	Answered	Number PD cases treated
Argentina	2	2	21
Brazil	60	55	1688
Chile	4	4	42
Colombia	4	4	238
Guatemala	1	0	not informed
Honduras	1	0	not informed
Mexico	8	8	541
Panama	1	0	not informed
Paraguay	1	1	9
Peru	1	1	4
Uruguay	1	1	79
Total	84	76	2682

health care system and in 56,6% to have it paid by health care insurance companies.

Table 2 shows types of PD treated by LARPD centers with CRS with HIPEC. In 99,7% a multidisciplinary team treats PD. 88,2% of the centers pointed out the necessity of a more experienced center supervising a center that is starting a CRS with HIPEC program. There was 100% agreement that CRS is the most important aspect in increasing survival rates in patients with PD, meaning an optimal CCO CRS. 82,9% of the centers considered that an optimal CCO CRS is more important than a rigid protocol to define the order of tumor sites to be operated. And to obtain CCO CRS, the sequence of areas to have tumors resected should depend on the experience of each surgical team.

All centers considered essential to have surgeons in their team who are trained to perform complex multiviscerous resections and lymphadenectomies.

Considering clinical aspects for selection of best patients suitable to be submitted to CRS with HIPEC, 94,7% of the centers indicated that patients should have ECOG Performance Status - PS 0 or 1; 45,3% to be up to 75 years old and 61,3% that body mass index should not be a contraindication.

All centers use PCI [20] to determine the extension of PM. Regarding the exam of choice to assess the extent of PM, 85,3% indicated CT scan as fundamental and 81,8% indicated MRI as a useful tool. 62,7% use laparoscopy when imaging exams are not able to define the extent of PM. To evaluate the presence of extraperitoneal metastasis, 72,6% indicated CT scan and 60% PET-CT as fundamental, while 80,9% indicated MRI as a useful tool.

LA centers indicated serum markers that are required to be used as postoperative evaluation of optimal cytoreduction and recurrence. CEA is used in peritoneal pseudomyxoma by 65,3% of the centers. In colorectal cancer, CEA is used in 97,3% and CA 19.9 in 69,2% of the centers. For gastric cancer, CEA is used in 60% and CA 19.9 in 69,2%. CA 125 is used in 90% of the centers for epithelial

Table 2

Types of Peritoneal Diseases treated using cytoreductive surgery with HIPEC by the 76 Latin American centers.

Type of peritoneal disease	Centers that have treated	Number of cases treated
Pseudomyxoma	92,1%	941
Colorectal cancer	82,9%	592
Mesothelioma	77,6%	129
Ovarian cancer	72,4%	602
Gastric cancer	47,4%	113
Sarcoma	11,8%	17
Other cases	9,2%	288
Total		2682

HIPEC: hyperthermic intraperitoneal chemotherapy.

ovarian cancer. LA centers are not using serum markers for peritoneal mesothelioma and sarcomas.

There was no agreement if digestive tract anastomosis should be performed before or after the HIPEC phase. 25,3% of the centers perform anastomosis before HIPEC; 41,4% after HIPEC and 33,3% answered that the moment of the anastomosis depends on the case. Peritoneal dialysis solution is used by 77,3% of the centers to deliver HIPEC; 96% use the abdomen temperature between 40 to 43 °C; closed perfusion is used in 81,3%. Peritoneal solution flow rate between 600 and 1500 ml/min is used in 77,3%; the parameter of 2–3 L/m² is used by 62,7% of the centers to calculate the total volume of solution to be used in the abdominal cavity for the hyperthermic peritoneal perfusion. Laparoscopic CRS with HIPEC is not indicated by 84,1%, even in cases of low PCI. 73,6% of the centers perform washout of the peritoneal chemotherapeutic solution from the abdomen after HIPEC.

Patients hemodynamic instability (98,7%), coagulation disorder (96%) and surgical complications (69,3%) were indicated as situations not to perform HIPEC after CRS. When HIPEC is not performed after optimal cytoreduction, 61,3% of the centers consider a second surgical intervention to perform it. A 30% chemotherapeutic HIPEC dose reduction is performed in 68% of the centers in cases of extensive cytoreduction or when debilitated patients are treated, in which a possible increase in surgical morbidity and mortality is anticipated by patients' clinical condition. Regarding the use of antibiotics in CRS with HIPEC, 46,7% of the centers maintain it for 24 h and 38,7% for 48 h after the procedure.

Peritoneal mesothelioma

All LARPD's centers recommend CRS with HIPEC for the treatment of peritoneal mesothelioma. Optimal CRS for mesothelioma was considered by 51,5% of the centers to be the resection specifically of the tumor affected regions (selective peritonectomy); 33,82% of the centers perform complete parietal peritonectomy and 14,7% perform selective peritonectomy in patients with good prognosis and complete parietal peritonectomy in cases of poor prognosis. 61,7% of the centers perform lymphadenectomy only if lymph nodes metastasis is suspected. Formal contraindications to the treatment of peritoneal mesothelioma with CRS with HIPEC were incomplete CC2 CRS (59,7%) and extraperitoneal disease, including pleura (77,6%) and liver metastases (65,7%). The most used protocol is in Table 3.

Pseudomyxoma peritonei

All centers consider CRS with HIPEC as the standard treatment of pseudomyxoma peritonei. 52,2% indicated that the terms

Disseminated Peritoneal Adenomucinosis (DPAM), Peritoneal Mucinous Carcinomatosis (PMCA) and Intermediate or Discordant feature group (PMCA-I/D) [21] could be used for its histological classification. 43,5% consider Low-Grade Mucinous Carcinoma and High-Grade Mucinous Carcinoma [22] as a better classification.

There is no role for neoadjuvant chemotherapy, even in high-grade neoplasia, for 52,9% of the centers. Systemic adjuvant chemotherapy after optimal CRS with HIPEC should only be delivered in high grade tumors according to 57,1% and in case of lymph node metastasis to 37,1%.

When there is extraperitoneal metastatic disease, 55,7% do not indicate CRS with HIPEC and 44,3% indicate it only if metastases are resectable. Specifically in cases of pleural metastases, 46,4% consider the patient ineligible for CRS with HIPEC. On the other hand, 43,5% perform optimal CRS of abdominal and pleural metastasis and include the thoracic cavity in the HIPEC with the open diaphragm, while 10,1% perform only palliative CRS without HIPEC. High PCI is not a contraindication for CRS with HIPEC for pseudomyxoma as 82,9% perform the procedure regardless the PCI if CC0/CC1 CRS is obtained. Palliative CRS without HIPEC is indicated by 76,8% in symptomatic patients. The most used protocols are presented in Table 3.

When asked what to do in a patient submitted to appendectomy with incidental findings of small amount of gelatinous acellular material around the appendix and histopathological report indicating a 0,5 cm high grade mucinous neoplasia with clear margins, 38,6% answered they would follow up with imaging exams and perform CRS with HIPEC only in case of recurrence. 31,4% would perform a second laparoscopy and deliver HIPEC if presence of mucin in the abdominal cavity is found. 18,6% would perform a right colectomy with HIPEC.

Prophylactic HIPEC in patients with epithelial appendiceal neoplasms without mucin in the cavity should not be performed according to 79,7%.

Ovarian cancer

76,1% of LARPD's centers indicate CRS with HIPEC to selected cases of ovarian cancer. CRS with HIPEC should only be considered in patients with PM of epithelial ovarian cancer in 91,7% of LARPD's centers. The best time to indicate this therapy in patients with PM from epithelial ovarian cancer for 46% of the centers is after neoadjuvant chemotherapy, while for 77,8% it is after recurrence in platinum-sensitive patients. 50,8% indicate CRS with HIPEC in recurrent platinum-resistant patients. Table 3 shows the most indicated protocols.

Absolute contraindication for CRS with HIPEC were the presence of extraperitoneal disease for 76,2% and more than 3

Table 3

Best protocols for cytoreductive surgery with HIPEC in the treatment of peritoneal disease considered by the 76 Latin American centers.

Peritoneal Disease	HIPEC	Intravenous chemotherapy ^a	% ^b
Mesothelioma	Cisplatin 50 mg/m ² + Doxorubicin 10–15 mg/m ² 60 min [26]	None	56%
Pseudomyxoma	Mitomycin C 35 mg/m ² 60–90 min ^c [27]	None	81%
Pseudomyxoma	Oxaliplatin 360–460 mg/m ² 30 min [27]	5FU 400 mg/m ² + LV 20 mg/m ²	45%
Ovarian platinum-sensitive	Cisplatin 75–100 mg/m ² 60–90 min [28]	None	90%
Ovarian platinum-resistant	Doxorubicin 35 mg/m ² + Paclitaxel 175 mg/m ² 60 min [11]	None	75%
Colorectal	Mitomycin C 35 mg/m ² 90 min [27]	None	68%
Colorectal	Oxaliplatin 360–460 mg/m ² 30 min [27]	5FU 400 mg/m ² + LV 20 mg/m ²	57%
Gastric	Oxaliplatin 360–460 mg/m ² 30 min [13]	5FU 400 mg/m ² + LV 20 mg/m ²	53%
Sarcoma	Cisplatin 50 mg/m ² + Doxorubicin 15 mg/m ² 60–90 min [14]	Ifosfamide 1,300 mg/m ²	80%

HIPEC: hyperthermic intraperitoneal chemotherapy. 5FU: 5-fluorouracil. LV: leucovorin.

^a Intravenous chemotherapy delivered during HIPEC phase.

^b Percentage of the indicated protocol regarding only centers that treat the specific type of peritoneal disease.

^c Not exceeding the total intraperitoneal dose of 70 mg.

resectable liver metastases for 59,7% of LARPD centers. Patients with PCI of 15 or less were considered the best suitable for CRS with HIPEC for 40,3%. If an optimal CCO/CC1 CRS is obtained, 56,4% perform HIPEC even with higher PCI. 98,4% consider that best results of CRS with HIPEC are obtained when a CCO CRS is achieved. Although 83,6% of centers would deliver HIPEC even if a CC1 CRS is accomplished. Only 1,7% of the LARPD's would deliver HIPEC if CC2 is the best CRS possible. If there is not the possibility of an optimal CRS (CC0/CC1) but the patient has proper clinical status, 74,6% considered adequate to indicate intravenous chemotherapy with further evaluation; if there is tumor regression, another laparotomy with the intent of CRS with HIPEC should be considered. A second CRS with HIPEC is indicated in 63,5% of LARPD's centers. Palliative HIPEC aiming at the treatment of refractory ascites is considered in 54%.

Colorectal cancer

All centers consider CRS with HIPEC as a treatment option in selected cases of colorectal PM. Table 3 shows the most indicated protocols. In eligible patients, in which PM of colorectal adenocarcinoma is detected at the same moment of the primary colorectal tumor, 36,9% perform CRS with HIPEC as upfront treatment followed by the best systemic chemotherapy. 32,3% deliver the best systemic chemotherapy first and perform CRS with HIPEC even if no evidence of PM is detected at laparotomy. 30,7% delivers best systemic chemotherapy first and CRS with HIPEC only if persistence of PM is detected, only the primary tumor is resected if no PM.

When there is metachronous PM, upfront indication of CRS with HIPEC raises to 44,4%. There is still an inconsistency in HIPEC indication when upfront systemic chemotherapy is delivered as 34,9% would perform HIPEC even if no evidence of PM is detected in surgery and 20,6% would only perform it with persistent PM.

In patients with peritoneal and hepatic metastasis of colorectal adenocarcinoma and eligible for treatment with CRS with HIPEC, 84,3% indicate that systemic chemotherapy should be the initial treatment. Among those who indicate HIPEC after initial systemic chemotherapy, 43,7% would perform HIPEC only in the persistence of PM, against 40,6% who would deliver it regardless the presence of PM.

Absolute contraindications for CRS with HIPEC were PCI greater than 20 for 69,2% and more than 3 synchronous liver metastases for 46,9% of the centers. In terms of the PCI's upper limit to indicate CRS with HIPEC, 40% considered 15 and 41,5% considered 20.

HIPEC should be considered an adjuvant treatment for patients with colorectal adenocarcinoma at elevated risk of developing PM according to 60% of the centers, which would consider its indication in patients with positive peritoneal cytology (88,1%), perforated tumors (88,1%) and pT4 tumors (76,2%).

Gastric adenocarcinoma

CRS with HIPEC was considered a treatment option for 78,8% of LARPD's centers in highly selected gastric adenocarcinoma patients, with stable disease after systemic chemotherapy when image exams and laparoscopy do not indicate cancer progression. Centers that consider the use of CRS with HIPEC in gastric adenocarcinoma indicate it in patients with positive cytology (79,2%), PCI less than 6 (60,4%) and ovarian as the only site of metastasis 49,1%. Table 3 shows the most indicated protocol.

Sarcomas

80,9% of LARPD's centers consider that selected cases of PM can be treated with CRS with HIPEC. The indications for the procedure

were CCO/CC1 CRS (88,2%), with PCI less than 15 (52,9%) and when extra abdominal metastasis is excluded by CT scan or PET-CT (41,2%). Table 3 shows the most indicated protocol.

Discussion

These results are not evidence-based new data in CRS with HIPEC treatment neither a standard of care guideline but indicate the current practice of LA centers that are treating patients with CRS with HIPEC. It is the first step in the objective of standardization of PD treatment in LA. The participation of 76 centers that have delivered CRS with HIPEC in 2682 patients, in 8 LA countries, gives a strong fidelity and conformity of the results with the title and objective of this manuscript.

Despite the current indication of CRS with HIPEC as the standard treatment for peritoneal mesothelioma [4,5] and pseudomyxoma [1–3], and as an option that increases the survival of patients with PM of colorectal [7,8,23], and ovarian [12] cancers, judicial process is still required in 52,6% of the centers to have the procedures paid by the government public health care system and in 56,6% to have it paid by health care insurance companies. This fact points out the necessity of having LA public health authorities aware of the benefits of CRS with HIPEC in the treatment of PD to make the treatment accessible for all patients without the inconvenience and time-consuming demanded by a lawsuit.

LA centers are well acquainted with the technical aspects and are concerned with the safety and efficacy in delivering CRS with HIPEC. Important aspects regarding multidisciplinary, safe and best protocols are well identified in the results. These aspects can be recognized by the necessity of more experienced centers to guide the less ones when starting the CRS with HIPEC protocols. That a well performed CRS is the most important feature in achieving best results. Also, in the necessity of skilled surgeons in multiviscerous resections and lymphadenectomies to be the ones to provide CRS with HIPEC. And in the fact that the most indicated protocols are based in international standards [24,25]. It is also recognized in the definition of HIPEC contra-indication: patient's hemodynamic instability, coagulation disorder or surgical complication. A 30% chemotherapeutic HIPEC dose reduction to prevent surgical morbidity and mortality related to the procedure, indicated by most of the centers, in cases of extensive cytoreduction or when debilitated patients are treated, is similarly a clear concern in the safety of patients submitted to CRS with HIPEC.

As mitomycin C has not been available anymore in Brazil and as 55 of the 76 LARPD centers that participated in this survey are from Brazil, there are well indicated protocols that have been used to replace its absence.

Some issues related to the best moment to deliver CRS with HIPEC did not achieve consensus but also do not have guidelines in published data. These results point to the direction that the LARPD data base, that is being built up, is crucial to indicate patients who could benefit the most from CRS with HIPEC. As the LARPD data base is created, all cases treated by the 84 centers will be integrated with information that certainly will answer some of the controversial issues that were shown in this survey's results regarding the best moment and best patients to deliver CRS with HIPEC. LARPD's data base will show the outcome of each selected indication and protocol, providing answers to when and to whom CRS with HIPEC should be delivered.

Conclusions

This publication describes how LA centers are treating patients with PD. Further attempt will be the standardization of LA protocols of CRS with HIPEC that will certainly provide best therapeutic

options for patients with PD. Other important step will be to create the LARPD database, including all PD treated cases. Follow up results provided by this LARPD's data base, regarding relapse and survival rates, will answer some of the issues identified in this first publication concerning the best moment and best patients to indicate CRS with HIPEC.

Conflict of interest

All authors do not have conflict of interest.

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Appendix

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