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Review Article

A proposal of Brazilian Society of Surgical Oncology for standardizing cytoreductive surgery plus hypertermic intraperitoneal chemotherapy procedures in Brazil: pseudomixoma peritonei, appendiceal tumors and malignant peritoneal mesothelioma

Proposta de padronização da Sociedade Brasileira de Cirurgia Oncológica para procedimentos de citorredução cirúrgica e quimioterapia intraperitoneal hipertérmica no Brasil: pseudomixoma peritoneal, tumores do apêndice cecal e mesotelioma peritoneal maligno

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ABSTRACT

Cytoreductive surgery plus hypertermic intraperitoneal chemotherapy has emerged as a major comprehensive treatment of peritoneal malignancies and is currently the standard of care for appendiceal epithelial neoplasms and pseudomyxoma peritonei syndrome as well as malignant peritoneal mesothelioma. Unfortunately, there are some worldwide variations of the cytoreductive surgery and hypertermic intraperitoneal chemotherapy techniques since no single technique has so far demonstrated its superiority over the others. Therefore, standardization of practices might enhance better comparisons between outcomes. In these settings, the Brazilian Society of Surgical Oncology considered it important to present a proposal for standardizing cytoreductive surgery plus hypertermic intraperitoneal chemotherapy procedures in Brazil, with a special focus on producing homogeneous data for the developing Brazilian register for peritoneal surface malignancies.

Keywords: Injections. Intraperitoneal. Hyperthermia, Induced. Drug Therapy. Peritoneal Neoplasms.

INTRODUCTION

Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has emerged as a major comprehensive treatment of peritoneal surface malignancies, especially for malignancies that remain confined to the abdominopelvic cavity with little invasion of the underlying organs and no metastatic spread[1]. This multimodal approach has proved to be an effective curative treatment or a salvage therapy for a number of patients suffering from peritoneal surface malignancies[2,3] and is currently the standard of care for appendiceal epithelial neoplasms and Pseudomyxoma peritonei (PMP) syndrome[4,5] as well as diffuse malignant

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peritoneal mesothelioma (DMPM)[6,7]. The rationale of combining heat with intraperitoneal chemotherapy is the added benefit of the synergistic effect of heat and cytotoxic drugs[8]. This approach allows full peritoneal chemotherapy perfusion and exposure of poorly vascularized tumoral tissue in the abdomen with high concentrations of cytotoxic agents before the formation of adhesions that might limit peritoneal fluid circulation. The blood-peritoneal barrier limits the passage of these high doses into the plasma and reduces the risk of systemic toxicity. Heat itself has a direct cytotoxic effect; it also enhances the effect of certain antimitotic agents (i.e.: mitomycin C, cisplatin, oxaliplatin) as well as increases their penetration into tumor tissue[8,9]. Some studies also reveal that hyperthermia can reduce the mechanisms of cellular resistance to cisplatin[10] and induce an efficient anticancer immune response via exposure of cell surface heat shock proteins[11,12]. Furthermore, this technique is delivered intraoperatively, avoiding the need for implantation of peritoneal access devices, hence reducing catheter-related morbidity[13,14].

In Brazil, the management strategies by peritoneal surface malignancies with CRS/HIPEC have increased by efforts of the Brazilian Society of Surgical Oncology (BSSO) and its members. Following some pioneering initiatives, CRS/HIPEC continued to gain interest throughout the country and several reports of initial or consolidated experiences have shown the efficacy of this treatment in Brazil[15-29].

In summary, these data are heterogeneous in terms of technical particularities and antimitotic agents, but this combined therapeutic approach has been performed with acceptable morbimorbidity and mortality and appears to provide a survival benefit over conventional treatments in many of our centers. In these settings, the BSSO points out that no single technique has so far demonstrated its superiority, and several variations in techniques have produced heterogeneous and no comparable results, which require some standardization of practices that might permit systematic comparisons[30]. Thus, we considered it important to present a statement produced by BSSO in order to guide the current clinical practice concerning CRS/HIPEC procedures in Brazil, with a special focus on producing homogeneous data for the developing Brazilian register for peritoneal surface malignancies.

METHODS

Development Process

This proposal for standardizing HIPEC procedures addresses the following clinical points: 1) common technical aspects; 2) patients selection; 3) intraperitoneal chemotherapy schedules; and 4) perioperative oncological management. The BSSO Committee on Peritoneal Surface Malignancies and HIPEC were asked to consider the available evidence, contribute to the development of recommendations, provide a critical review, and finalize this proposal. Initially, few members (i.e.: the first four listed authors) of this committee were responsible for performing a non-systematic review of the most relevant scientific literature and writing a core proposal of standardization. Thereafter, all members reviewed the former version for discussion and improvements, and approved an ultimate version. An external review was also required from three invited experts in CRS/HIPEC procedures from outside Brazil (i.e.: Sugarbaker PH, Verwall VJ and Deraco M), just before submission for editorial review and consideration for publication.

Due to the lack of high-level evidence for all specific points to be addressed, recommendations were made based on large clinical experience and expert options. For technical aspects, proposals of standardization also considered results from a recent survey undertaken by the BSSO concerning the development of CRS/HIPEC procedures throughout our country. Accordingly, the use of words like "must" (or "must not") and "should" (or "should not") indicates that a course of action is proposed based on proportional levels of agreement amongst large clinical experiences and expert options, whereas the words "recommend" and "suggest" were also applied in a similar manner.

Disclaimers

The information herein provided by the BSSO should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. The information addresses only the

topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases, and is not intended to substitute for the independent professional judgment of the treatment provider, as the information does not account for individual variation among patients. Thus, the use of this information is voluntary and BSSO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Conflicts of Interest

All members of the committee were asked to list any conflicts of interest and to complete the journal's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of this proposal for standardization. In accordance with this policy, all members of this BSSO committee did not disclose any relationships constituting a conflict under the policy.

PROPOSAL FOR STANDARDIZING PROCEDURES

Patients Selection

Careful patient selection is the cornerstone for the management of peritoneal surface malignancies and must involve a comprehensive evaluation considering clinical, radiological, laboratory and histological findings. The suggested minimal preoperative investigations include: 1) physical examination; 2) cardiopulmonary investigation with cardiac echography and functional pulmonary exploration; 3) renal function investigation by creatininemia and clearance of creatinine; 4) biological evaluation of the hepatic function; 5) evaluation of nutritional state by body mass index and albuminemia; and 6) extent of disease and staging by contrast-enhanced multisliced computed tomography and, if necessary, FDG-PET, magnetic resonance imaging or laparoscopic exploration[31,32]. Tumor markers are also helpful and should be considered on the workup[33]. There is also an overall consensus that patients fit for a major comprehensive oncological approach such as CRS/HIPEC are those ASA I-II, performance status of 0-2, with no limiting comorbidities and aged lower than 65-70 years[31,34,35].

Preferentially, an experienced pathological team should review the preoperative clinical and histological findings for a proper diagnostic confirmation. Reports of pathological findings for PMP should be in line with the Consensus for Classification and Pathologic Reporting of Pseudomyxoma Peritonei and Associated Appendiceal Neoplasia by the Peritoneal Surface Oncology Group International (PSOGI)[36] and standards of the 7th edition of the AJCC staging classification, as appropriated[37].

Due to its rarity, review by an expert pathologist using a panel of at least two positive and two negative immunohistochemical stains is required to make a definitive diagnosis of DMPM. The specific panel depends on the differential diagnosis, but common positive markers include calretinin, D2-40, CK 5/6, and WT-1, and some frequently used negative markers include MOC-31, PAX8, BG8, Ber-EP4, B72.3, CEA, and CDX-238,39. Accordingly, these peritoneal tumors should be staged by the tumor-node-metastasis (TNM) system proposed by the PSOGI based on analysis of a multi-institutional database[40], whereas two distinct pathologic subtypes of borderline malignant potential named well-differentiated papillary mesothelioma (WDPM) and benign multicystic mesothelioma (BMM) that are much more common in the peritoneum than in the pleura should also be well recognized before treatment planning because of their better outcomes[38].

Patients with DMPM of histological biphasic or sarcomatoid subtype must not be considered for treatment with CRS/HIPEC6 as well as those tumors with high expression of Ki67 (i.e.: =25% by immunohistochemical evaluation)[41] that are usually

diagnosed under a high tumor load. Similarly, patients with both Ki-67 > 10 % and PCI > 17-20 are also unlikely to benefit from the procedure and should be considered for other treatment protocols[41-43].

The extent of peritoneal spreading represents one of the most important prognostic factors and the tumor burden as estimated by PCI (peritoneal cancer index) provides a good probability of achieving a complete cytoreduction during CRS for peritoneal malignancies. However, more than the tumor burden, the distribution of peritoneal spreading in the abdomen constitutes the principal limitation for performing CRS[31]. In these settings, the most frequent contraindications for CRS/HIPEC are extra-abdominal metastasis, massive involvement of the small bowel and its mesentery, hepatic pedicle and gastro-hepatic ligament, gross retroperitoneal lymph node involvement, and ureteral or biliary obstruction, whereas a restrictive cut-off value for PCI (i.e.: PCI >20) also should not be applied as an absolute exclusion criterion for CRS/HIPEC suffering of PMP[31,44,45].

Common Technical Aspects

Techniques of advanced CRS were previously standardized and described by Sugarbaker and must be followed accordingly with minimal variations of procedures[46-48]. On the other hand, several techniques of HIPEC have been described since its first use in the 80's[49]. Variable particularities of HIPEC include installation circuit, timing of visceral anastomoses (i.e.: before or after HIPEC), length of perfusion, target temperatures, type and volume of perfusate, and others. Herein, a started point of discussion is performing HIPEC as a closed or open abdominal (coliseum) technique. Whilst there are no convincing data favoring any technique[50-52], we have chosen for the use of a closed technique based on the simplicity of this method and decreased contamination risk[53], as well as because most of the centers perform closed HIPEC procedures in Brazil. In these settings, we also propose a minimum of 4L (ranging from 4-6L) of perfusate into the abdominal cavity in order to counterbalance the theoretical drawbacks of closed techniques in comparison to the open approach since a maximal distention of the abdomen enhances the thermal homogeneity throughout the peritoneal cavity[54] and facilitates drug distribution into the whole abdomen, ensuring that every site of the diffuse peritoneal disease receives the optimal treatment. At this point, we also suggest an inflow temperature of 44°C in order to maintain a critical threshold for potentiating cytotoxic chemotherapy of above 40°C into the peritoneal cavity[55], with an optimal range of 41-43°C as average between in- and out-drains. In regards of flow rate parameters, our purpose is that 300-500mL/min should be applied during the "patient-filling phase" and thus increased to 700mL/min during the "circulation" and "HIPEC" phases[56-58]. Similarly, as carrier solutions, we suggest the use of 1.5% dextrose isotonic peritoneal dialysis solutions for any drug protocol proposed[53] here, even for those oxaliplatin-based schedules[59,60]. Because the main risk of HIPEC is related to direct or indirect skin exposure to antiblastic drugs, the use of two pairs of gloves should be mandatory to protect the surgical team during abdomen manipulation after the "emptying phase"[61-63].

In the light of reducing morbidity related to CRS, we point out that right hemicolectomy is not routinely required in PMP resulting from mucinous appendiceal neoplasms at low risk of relapse or lymph node involvement[64,65], and that a more conservative approach confining the peritonectomy to where there is evidence of more solid disease is also a suitable approach for PMP/Appendiceal Tumors[66]. On the contrary, we suggest a complete parietal peritonectomy in patients with DMPM based on a controlled study conducted by Baratti *et al.*[67] demonstrating improved sur-

vival outcomes after the radical approach. Another main controversial issue concerning the technical aspects of CRS is the timing of bowel anastomoses. Recently, the BSSO developed an online survey involving the technical aspects of CRS/HIPEC and achieved no consensus in regards to this issue applying a simplified two-round-based Delphi method, in spite of the fact that previous reports from the *5th International Consensus Metting on Peritoneal Surface Malignancies Treatment* had favored the "after HIPEC" approach (54%) for the closed abdomen technique[66]. Due to the lack of evidence to support a strong recommendation, we propose that intestinal anastomoses should be performed before HIPEC based on no reports of recurrence involving the anastomotic area as an isolated or first site of relapse and because of the lower time of chemotherapeutic exposure for the surgical team. Further, in cases requiring an esophago-jejunal anastomosis after total gastrectomy, this approach may also reduce the exposure of mediastinum to cardiotoxic drugs as cisplatin. In a similar manner, a diverting ileostomy is not routinely recommended and may be avoided at the surgeon's discretion after colorectal stapled anastomoses[68], especially because restoration of bowel continuity is often related to high rate of temporary stomas that will not be subsequently reversed[69] as well as to postoperative complication[70].

Perioperative care practices for CRS/HIPEC are widely variable nationally and internationally and standardization of such practices offers an opportunity to incorporate experience from high-volume centers and may enhance patient outcomes[30]. In these settings, one of the most recent reviews involving several aspects related to peri, intra and postoperative management of patients undergoing CRS/HIPEC have just been published by Raspé *et al.*[53] and summarizes the main understanding of this *committee* to improve periopertive care standards for the procedures. Following these review of evidences, we highlight that a goal-directed fluid therapy using noninvasive monitoring tool of hemodynamic parameters improves outcome in terms of major abdominal and systemic postoperative complication incidences or length of hospital stay compared with the standard approach[71,72]. We also maintain that implementation of fast-track protocols are feasible in order to accelerate recovery, reduce morbidity and shorten convalescence to ultimately improve outcomes and reduce costs, especially for those patients with low PCI not requiring digestive anastomosis[53,73-75]. Our proposal is also along the line that ICU stay directly following CRS/HIPEC should be preferably based on the extent or resections performed and individual patient characteristics and risk factors[76]. Similarly, patients with peritoneal carcinomatosis should be considered as a complex oncological group at high risk of infectious complication - the most important cause of peri-operative morbidity and death in CRS/HIPEC[77]. Thus, we recommend ampicillin/sulbactan[78] or cefoxitin over 24-72hs as antibiotic for infection prophylaxis, preferably as short-course regimens of 24h[78], while the use of antibiotic for therapeutic purpose should be guided by culture and sensitivities. On the other hand, the association of antimycotics should be indicated only when a fungal infection was presumed in the presence of neutropenia/fever or normal leukocytosis and neutropenia in patients with fever[73,78,79]. We also recommend vaccinations to reduce the risk of sepsis for patients in which splenectomy is presumable during CRS/HIPEC. These patients should receive pneumococcal and influenza immunization; patients not previously immunized should also receive *Haemophilus influenza* type B and meningococcal group C conjugate vaccines[80,81]. As much as possible, especially because splenectomy increases major complication rate in patients undergoing CRS/HIPEC, we suggest this vaccine should be given at least two weeks before or 14 or more days after procedures[82].

Regarding the classification systems to be used for reporting complications related to CRS/HIPEC, we follow the statement from the 5th International Consensus Metting on Peritoneal Surface Malignancies Treatment to adopt the joint NCI/NIH Common Terminology Criteria for Adverse Events (CTCAE), last version[83]. However, because of different interpretations of severity grades of complications after CRS/HIPEC between this system and the therapy-oriented Clavien-Dindo classification[84] - a universally-accepted classification in many surgical fields - we suggest that complications should be reported in both of these systems in order to permit comparison amongst different studies as well as with other comprehensive oncological and surgical procedures. As previously reported in the Milan consensus, the peritoneal cancer index (PCI) and the completeness of cytoreduction (CC) score described by Sugarbaker have been the recommended systems for intraoperative staging and classification for residual disease size, respectively since these experienced surgeons' naked-eye estimations were considered the ideal methods of assessment by the large majority of experts[85,86].

Intraperitoneal Chemotherapy Schedules (Table 1)

Even though several regimens of drugs for HIPEC procedures are available, we suggest the following options for treatment of DMPM: (1) cisplatin 100mg/m^2 plus doxorubicin 15mg/m^2 or (2) carboplatin 800mg/m^2, both for 60min at 4L of perfusate[56,87]. For *PMP* and appendiceal tumors, the suggested protocols are (1) oxaliplatin 360mg/m2 for 30min or (2) cisplatin 100mg/m^2 plus doxorubicin 15mg/m^2 for 60min, both at 4L of perfusate[56]. These drug dosages should be reduced by about 30% for patients over the age of 60-70 years, patients previously exposed to multiple lines of systemic chemotherapy, patients who needed GM-CSF rescue for febrile neutropenia while on systemic chemotherapy, patients who have received radiation therapy to bone-marrow bearing regions, and those who underwent extensive surgical cytoreduction due to high PCI scores[88,89]. Accordingly, special attention is required for dose reduction of oxaliplatin to 200-250mg/m^2 in these cases because of the increased risk of postoperative hemorrhagic complications compared with HIPEC and other drugs90. For safety reasons, we point the dose limiting of 1000mg/m^2 (or 200mg/m^2/L of perfusate) for carboplatin, total dose of 240mg (or 45mg/L of perfusate) for cisplatin, 15mg/L of perfusate for doxorubicin, and 460mg/m^2 for oxaliplatin[56,87].

A major point concerning the proposed intraperitoneal chemotherapy schedules for CRS/HIPEC procedures in Brazil is the current unavailability of mitomycin (MMC) in our country due to commercial matters. However, even though some data suggest that MMC might be a better agent for HIPEC delivery than oxaliplatin in patients suffering of peritoneal carcinomatosis of colorectal origins with favorable histologies and low burden of disease (i.e.: PSDSS I/II)[91], contrary data also suggests that oxaliplatin offers a survival advantage over MMC in similar settings[92], while a trend of better overall survival may also be noted in patients with unfavorable histologies and high burden of disease (i.e., PSDSS III/IV) treated with oxaliplatin[91]. In fact, the largest published data involving more than two thousand patients with *PMP*/appendiceal tumors treated by strategies of CRS/HIPEC in 16 specialized centers had demonstrated no significant benefit in terms of overall survival for HIPEC with Oxaliplatin vs. MMC (10y survival of 78% vs. 66%, respectively; differences not statistically significant)[4]. But other wide data suggests that the use of oxaliplatin does not significantly increase the overall perioperative morbidity and/or mortality rates compared to a mitomycin- and doxorubicin-based protocols[93]. In these settings, we alternatively suggest the use of oxaliplatin for HIPEC delivery in PMP and apendicecal

tumors especially because of the need for a lower perfusion time and the cisplatin plus doxorubicin protocol as an alternative lower-cost option. Similarly, due to the potential of increasing morbidity and complexity of procedures, we do not advocate the routine use of bidirectional oxaliplatin-based HIPEC regimens unless more convincing data could be available, or any intensification of the HIPEC protocol by adding irinotecan to the oxaliplatin-alone regimen[94].

Table 1. *Proposed chemotherapy schedules of HIPEC (closed abdomen technique) for treatment of Pseudomixoma peritonei (PMP) / Appendiceal Tumors and Diffuse Malignant Peritoneal Mesothelioma (DMPM).*

Disease	Intraperitoneal Chemotherapy Schedules
PMP*	Oxaliplatin 360mg/m^2, 30min at 4L of perfusate; or CDDP 100mg/m^2 plus doxorubicin 15mg/m^2, 60min at 4L of perfusate.
DMPM	CDDP 100mg/m^2 plus doxorubicin 15mg/m^2, 60min at 4L of perfusate; or Carboplatin 800mg/m, 60min at 4L of perfusate.

** Pseudomixoma peritonei (PMP) and appendiceal epithelial neoplasms.*

Perioperative Oncological Management

Perioperative oncological management involving systemic therapies for both of these conditions is not clearly supported by randomized controlled trials, but a review of data from experienced centers has provided some evidence to this issue. For DMPM, neoadjuvant chemotherapy was not associated with increased completeness of cytoreduction[95] and may impact negatively the survival for patients who underwent CRS-HIPEC with curative intent, whereas adjuvant chemotherapy may delay recurrence and improve survival[96]. Thus, we suggest that upfront CRS plus platin-based HIPEC should be considered the standard approach for DMPM, while waiting for a stronger level of scientific evidence[6,67,96]. Systemic chemotherapy should be administered principally in patients with recurrent disease or at a high risk for recurrence, and in those who are not appropriate candidates for aggressive surgery or were not optimally debulked[97]. For PMP from appendiceal origin, prior chemotherapy treatment was also found as independent predictors for a poorer progression-free survival and overall survival according to the largest international registry study exploring the strategy of CRS/HIPEC[4]. However, subset analysis of this same data had confirmed the peritoneal mucinous carcinomatosis histopathologic subtype as an independent predictor of a poorer overall and disease-free survival[4], in line with other reports that adenocarcinoma with signet ring cell and adenocarcinoid histomorphology contributes to the poor prognosis associated with peritoneal metastasis from appendiceal adenocarcinoma[98]. Herein, even though the possible benefit of neoadjuvant chemotherapy for high-grade tumors in general remains controversial[99,100], preoperative systemic chemotherapy appears to improve the prognosis of patients with signet ring cell histology[37], which suggests the need for some discussion in a multidisciplinary tumor board in order to decide about the best approach to each specific case. At this point, our recommendation is to consider the use of preoperative fluoropirimidine-based systemic chemotherapy for high-grade peritoneal metastasis from appendiceal adenocarcinoma with signet ring cell histology and moderate to high PCI scores[37,99]. In the adjuvant settings, the use systemic therapies should be guided by stands for other advanced colorectal cancers,

as appropriated.

Finally, regarding the use of early postoperative intraperitoneal chemotherapy (EPIC) in combination with CRS/HIPEC, our proposal of standardized procedures is not to routinely deliver EPIC for either PMP/appendiceal tumors or DMPM, since this additional procedure is associated with an increased rate of complications and no clear benefit in terms of survival[7,13,14], whereas HIPEC--alone protocols are much simpler for patient, surgeon, and nursing care[13]. As previously reported, the use of EPIC did not translate to better survival outcomes in the largest surgical series exploring CRS/HIPEC for the treatment of PMP/appendiceal tumors[4] or DMPM[6], which support the proposal being presented. Thus, this BSSO committee suggests the use of EPIC as an alternative treatment option for treatment of these both malignancies only when HIPEC is not available.

CONCLUSION

Practices of CRS/HIPEC are widely variable and standardization of such practices may enhance patient outcomes and improve care standards across all centers that offer this procedure in Brazil. Herein, we have reviewed the main worldwide variations for the treatment of PMP/appendiceal tumors and DMPM with CRS/HIPEC and thus proposed standards for common technical aspects, patient selection, intraperitoneal chemotherapy schedules and perioperative oncological managements. The effort of producing a nationally acceptable proposal to guide clinical practice concerning CRS/HIPEC procedures may contribute to producing homogeneous data that permits pooled analysis from the developing Brazilian register for peritoneal surface malignancies.

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R E S U M O

A cirurgia citorredutora com quimioterapia intraperitoneal hipertérmica emergiu como um importante tratamento das neoplasias peritoneais e é, atualmente, o padrão de atendimento para neoplasias epiteliais do apêndice associadas à síndrome de pseudomixoma peritoneal, bem como para o mesotelioma peritoneal maligno difuso. No mundo, existem algumas variações reconhecidas das técnicas de cirurgia citorredutora e quimioterapia intraperitoneal hipertérmica, entretanto nenhuma técnica até agora demonstrou sua superioridade sobre o outra. Portanto, a padronização destes procedimentos poderia melhorar a prática clínica e permitir a comparação adequada entre os resultados. Neste cenário, a Sociedade Brasileira de Cirurgia Oncológica considera importante a apresentação de uma proposta de padronização de procedimentos de cirurgia citorredutora com quimioterapia intraperitoneal hipertérmica no Brasil, com um foco especial na produção de dados homogêneos para o desenvolvimento do registro brasileiro das neoplasias peritoneais.

Descritores: Injeções Intraperitoneais. Hipertermia Induzida. Quimioterapia. Neoplasias Peritoneais.

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