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RESEARCH ARTICLE

AIOM RECOMMENDATIONS ON THE USE OF CYTOREDUCTIVE SURGERY AND HIPEC IN PRIMARY AND SECONDARY PERITONEAL TUMORS

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ABSTRACT

Peritoneal surface malignancies represent rare and hard-to-treat entities that include primarily abdominal that involve disseminating cancer cells into abdominal peritoneum, with or without associated extraperitoneal disease. Diagnosis and management of these aggressive cancers need a dedicated multidisciplinary team and a high-volume center for locoregional treatment where technically and clinically feasible.

This article summarizes the most updated evidence-based guidelines that the Italian Medical Oncology Association (AIOM) has implemented with a multidisciplinary panel of experts, including dedicated expert clinicians such as pathologists, surgeons, medical oncologists, and the support of methodologists, to guide clinicians involved in the

primary management of patients with peritoneal neoplasms in their daily clinical practice. Based on the type of studies addressing the questions and their methods, AIOM guideline methodologists used the GRADE method (Grading of Recommendations Assessment, Development, and Evaluation: GRADE) to classify the quality of each kind of evidence.
In selected cases, the main curative treatment consists of a cytoreduction surgery (CRS) that implies the complete removal of the macroscopically appreciable disease or any minimum residual millimeter. It is then associated with intraperitoneal chemo-hyperthermia (HIPEC), carried out at the end of the surgical demolition time, a particular type of chemotherapy that exploits the combined effect of heat and high concentrations of drugs, with a localized action in the area affected by the neoplasm.
We here provide recommendations for 6 main clinical scenarios: primary treatment of primary serous peritoneal papillary carcinoma, pseudomixoma peritonei, colorectal and gastric cancer, ovarian carcinoma, and peritoneal mesothelioma.

KEY WORDS

Peritoneal tumors; cytoreductive surgery; HIPEC; guidelines.

IMPACT STATEMENT

This paper represents a synthesis of 2021 clinical practice guidelines about presentation, diagnosis and management of primary and secondary peritoneal surface malignancies provided by an expert panel on behalf of AIOM.

INTRODUCTION

Peritoneal surface malignancies represent rare and hard-to-treat entities that include primarily abdominal (*e.g.*, appendiceal neoplasms or peritoneal mesotheliomas) or secondary tumors (from abdominal or gynaecological cancers) that involve the dissemination of cancer cells into abdominal peritoneum, with or without associated extraperitoneal disease. Ovarian cancer, mesotheliomas, primary appendiceal carcinomas, and other primary abdominal carcinomas (colorectal, gastric, or pancreatic) may cause peritoneal carcinomatosis. In such cases, the main clinical sign is malignant ascites: the accumulation of fluid results from blockage of the draining lymphatic channels (which generally keep the amount of intraperitoneal fluid low) and increased vascular permeability. Advanced cancer with peritoneal carcinomatosis may also cause in later stages diarrhea, constipation, nausea, abdominal pain, bloating, weight loss or gain, loss of appetite, or early gastric fullness.
In 2018 the Italian Medical Oncology Association (AIOM) published the first edition of specific clinical practice guidelines for primary and secondary peritoneal tumors (1), which were subsequently updated in 2020. This article summarizes the most updated evidence-based guidelines that the AIOM has implemented with a multidisciplinary panel of experts, including dedicated expert clinicians such as pathologists, surgeons, medical oncologists, and the support of methodologists, to guide clinicians involved in the primary management of patients with peritoneal neoplasms in their daily clinical practice. Based on the type of studies addressing the questions and their methods, AIOM guideline methodologists used the GRADE method (Grading of Recommendations Assessment, Development, and Evaluation: GRADE) to classify the quality of each kind of evidence. In particular, the GRADE method assesses methodological bias within the studies, uniformity between different studies results; consistency of results across different studies; repeatability of results on a broader patient sample set; the effectiveness of treatments. Treatment comparisons result in one out of four GRADE scores, reflecting the quality of the

STRONGNESS OF CLINICAL RECOMMENDATION	TERMS	MEANING
STRONG POSITIVE	Strong Positive "In patients with (selection criteria) the xxx intervention should be considered as a first intention therapeutic option".	The intervention in question should be considered as the first therapeutic option (evidence that the benefits outweigh the harm).
WEAK POSITIVE	"In patients with (selection criteria), the xxx intervention can be considered as a first intention therapeutic option, as an alternative to yyy".	The intervention in question can be considered as a first intention option, aware of the existence of alternatives equally feasible (uncertainty regarding the prevalence of benefits over damages).
WEAK NEGATIVE	"In patients with (selection criteria), the xxx intervention should not be considered as a first intention treatment option, as an alternative to yyy".	The intervention in question should not be considered as a first intention option; it could, however, be suitable for use in highly selected cases and after complete sharing with the patient (uncertainty regarding the prevalence of harm over benefits).
STRONG NEGATIVE	"In patients with (selection criteria), the xxx intervention must not be considered as a first intention therapeutic option".	The intervention in question must in no case be taken into consideration (evidence that the harm prevails over the benefits).

Table I. *Strongness of clinical recommendation graded in four levels based on clinical relevance.*

evidence: high-quality, moderate-quality, low-quality, or very low-quality evidence. The strength of the recommendation is graded, based on clinical importance, on four levels (**table I**).

The patient's clinical history greatly conditions the diagnostic classification of peritoneal neoplasms. Specifically, the cases in which a peritoneal neoplastic pathology is diagnosed during the follow-up of a known primary neoplasm should be distinguished from those in which the patient's medical history is mute. In the first case, the diagnostic process aims to verify the correlation between the metastatic event and previous cancer. In the second case, however, the diagnostic workout must be planned according to the invasiveness of the procedures and resources availability.

The diagnostic process must first consider the more frequent pathologies according to the sex and age of the patient. The other diagnostic elements that emerge from clinical evaluations, blood chemistry, and instrumental tests (tumor markers, computed tomography, PET-CT, MRI, endoscopies) must be integrated with the epidemiological data. The indication for the surgical, diagnostic procedure (laparoscopy or exploratory laparotomy) must be placed with extreme accuracy and if the other diagnostic procedures could not lead to the diagnosis of certainty (**figure 1**). These invasive procedures allow both the biopsy of neoplastic material and an accurate estimate of the extent of peritoneal disease using the Peritoneal Cancer Index (PCI). PCI is a value determined by the size of the peritoneal implants and the distribution of nodules on the peritoneal surface. For the evaluation of the final score, the size of the peritoneal nodules is first assessed; The sum of the lesion size score and the distribution of tumor in the abdominopelvic regions gives us the patient's PCI. Implants are scored as lesion size 0 through 3 (LS-0 to LS-3). LS-0: no implants are seen throughout the region; LS-1: implants visible up to 0.5 cm in greatest diameter; LS-2: nodules greater than 0.5 cm and up to 5 cm; LS-3: implants 5 cm or greater in diameter (2). However, it is not recommended to proceed with aggressive surgical attempts and debulking before a complete and correct diagnostic classification. Adverse events resulting from improper abdominal-pelvic surgical manipulation are worrisome. They include disseminating neoplastic cells in the surgical explored areas that remain trapped in fibrosis and fibrin and are may become poorly sensitive to systemic and local-regional chemotherapy treatments, inevitably leading to cell proliferation and neoplastic growth (3-7).

Cytoreduction surgery (CRS) implies the concept of surgical radicality with the complete removal

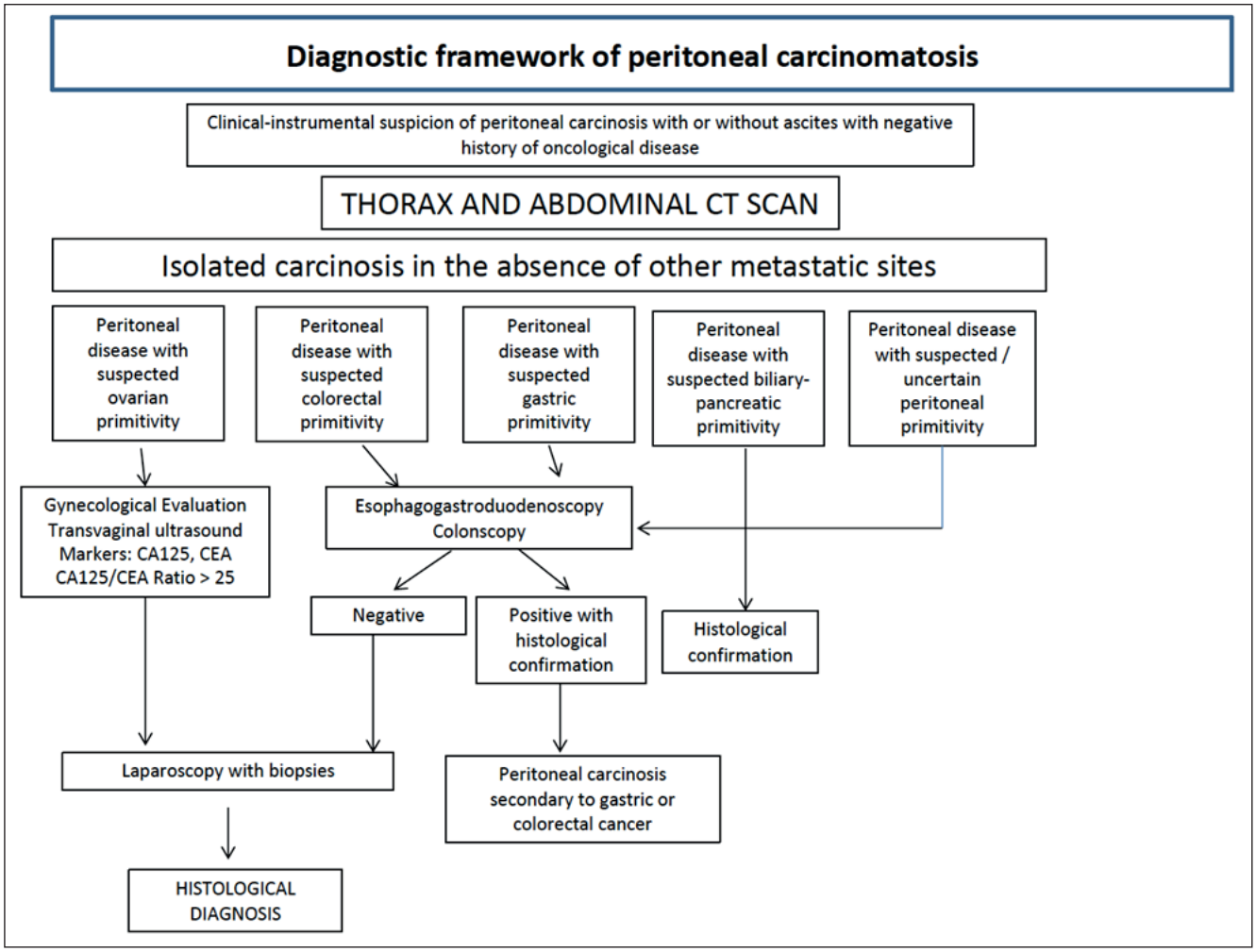

Figure 1. *Diagnostic workup of peritoneal carcinomatosis.*

of the macroscopically appreciable disease or any minimum residual millimeter. This concept differs from debulking, which implies palliative removal of part of the neoplastic disease with gross neoplastic residue. CRS for peritoneal tumors is a concept developed by Paul H. Sugarbaker (8). The completeness of Cytoreduction (CCR) is coded at the end of the surgical phase according to the criteria validated by the Consensus Conference of 2006 (9, 10). It represents the most important prognostic factor of peritoneal neoplasms and is expressed by cc-score: CC-0 (absence of visible residue), CC-1 (residue lower than 2.5 mm), CC-2 (residue greater than 2.5 mm and less than 5 cm), CC-3 (residue greater than 5 cm and with confluent nodules).

Intraperitoneal chemo-hyperthermia (HIPEC), carried out at the end of the surgical demolition time, represents a locoregional therapeutic aid, supplementary to the surgical intervention; its action is manifested in the moment of maximum cytoreduction of the neoplasm, in the absence of adhesions, and above all before the cells released in the abdomen are implanted on the bloody surfaces or are protected by the physiological deposition of fibrin and stimulated to proliferation by the chemical mediators of inflammation. It is a particular type of chemotherapy that exploits the combined effect of heat and high concentrations of drugs, with a localized action in the area affected by the neoplasm. It consists in the perfusion of the abdominal cavity with a variable quantity (3-6 liters) of liquid (Perfusate) in which high doses of chemotherapy are administered in conditions of hyperthermia. HIPEC is performed immediately after finishing the CRS by placing a system of cannulas through the abdominal wall connected to an extracorporeal circulation circuit. Therefore, the perfusate is circulated with chemotherapeutic agents in conditions of hyperthermia with a closed abdomen or an open abdomen. Duration of perfusion, type of chemotherapy and temperatures are a function of the histological type to be treated (11, 12).

RECOMMENDATIONS FOR CRS AND HIPEC

In patients with Primary Serous Peritoneal Papillary Carcinoma (SPPC), the neoadjuvant chemotherapy followed by HIPEC associated with CRS is indicated compared to chemotherapy treatment followed by interval debulking surgery? (table II)

SPPC is histologically similar to epithelial ovarian cancer (EOC) but clinically differs by a predominantly peritoneal widespread, with a little ovarian involvement. The epidemiological, clinical and molecular differences between SPPC and EOC have been highlighted and described in a review (13).
The exact incidence of SPPC is not clear, and actually, about 10-20% of EOC labeled as serous papillary ovarian carcinoma are SPPC.
Due to the similarities with EOC, SPPC has often been treated by surgery and systemic chemotherapy (sCT) containing platinum and taxanes. Therefore, a lot of data arises from small retrospective cohorts or case-control, comparing patients with SPPC and EOC. The median overall survival (mOS) of patients with SPPC is 21-42 months, shorter than EOC patients, with a progression-free survival (PFS) of 11-17 months (14-16).
The experience gained in other peritoneal neoplasms through CRS and HIPEC has motivated various groups to extend the indications also on SPPC as a primary peritoneal neoplasm. The rationale for this approach is based on the multifocality, polyclonality, and the high frequency of widespread peritoneal metastases of SPPC. The analysis of 36 patients with SPPC treated with CRS and HIPEC was conducted in France and Italy (17). In addition, 35 patients received platinum-based systemic adjuvant treatment. Morbidity and mortality were 20.6% and 5.6%, respectively. Five-year OS was 57.4% and DFS was 24% (median of 16.7 months).
A single-center analysis of 29 patients with SPPC homogeneously treated with neoadjuvant chemotherapy with 6 cycles of Carboplatin and Paclitaxel followed by CRS and HIPEC, after a median follow-up of 12 months, showed a 5-years OS of 64.9% (median not reached) (18, 19). Overall, grade III-IV surgical complication was seen in 4/22 (18%) patients; no post-operative mortality was observed. Median PFS was 32.9 months, and 5-year PFS was 33.2%. CRS was performed with total parietal peritonectomy and with HIPEC using a chemotherapy combination based on Cisplatin plus Doxorubicin at 43 Celsius degree of temperature for 90 minutes.
Based on these results, the absence of randomized studies comparing the integrated treatment to standard chemotherapy and surgical debulking limits the significance of the results. However, the benefit assessed as overall and progression-free survival of sCT plus CRS and HIPEC treatment and relatively limited adverse events compared to sCT and surgical debulking, get the judgment in favor of the benefit over the damage, but it must be discussed with the patient regarding the extension of the surgical treatment. Therefore, the panel provided a positive recommendation in favor of sCT plus CRS and HIPEC.

In patients with resectable pseudomyxoma peritonei, is HIPEC associated with cytoreduction indicated rather than surgical debulking and systemic chemotherapy?

The main supporting literature included the McBride, *et al*. study (20), which is a review and meta-analysis of 15 observational studies concerning the treatment of pseudomyxoma peritonei by CRS associated with HIPEC in various forms (EPIC, HIPEC, HIPEC + EPIC). Median survival at 3, 5, and 10 years was 77.85%, 79.5%, and 55.9%, respectively. The median complication rate (calculated across 14 studies) was 40%. Although the complication rate is not negligible, the panel believes that the benefit given by CRS associated with HIPEC is still higher than that provided by repeated debulking surgeries.
Based on these assessments and experience in the field, the AIOM panel unanimously judged the balance between risks and benefits deriving from the execution of CRS and HIPEC in resectable pseudomyxoma peritonei to be favorable and provided a weak positive recommendation in favor of intervention.

If operability and resectability criteria are met in patients with diffuse malignant epithelioid peritoneal mesothelioma, are cytoreductive and HIPEC procedures indicated compared to systemic chemotherapy?

In patients with peritoneal mesothelioma, the efficacy of the combined treatment with CRS and HIPEC is reported in numerous papers reported in the literature (21-24). In summary, the results offered by palliative chemotherapy alone with convention-

DISEASE	GRADE QUESTION	STAGE	TIMING	DRUGS USED	RECOMMENDATION
PRIMARY SEROUS PERITONEAL PAPILLARY CARCINOMA (SPPC)	In patients with SPPC, the neoadjuvant chemotherapy followed by HIPEC associated with CRS is indicated compared to chemotherapy treatment followed by interval debulking surgery?	III	After 3-6 cycles of systemic chemotherapy	Cisplatin	Weak positive
PSEUDOMYXOMA PERITONEI	In patients with resectable pseudomyxoma peritonei, is HIPEC associated with cytoreduction indicated rather than surgical debulking and systemic chemotherapy?	Intraperitoneal metastases (intra-abdominal disease only)	Upfront	Various*	Weak positive
PERITONEAL MESOTHELIOMA (EPITHELIOID HISTOLOGY)	In patients with diffuse malignant epithelioid peritoneal mesothelioma, if operability and resectability criteria are met, cytoreductive and HIPEC procedures are indicated compared to systemic chemotherapy?	All stages (operable stage I-II disease or stage III after primary CT)	Upfront	Cisplatin-based*	Weak positive
OVARIAN CANCER (HIGH-GRADE SEROUS HISTOLOGY)	In patients with high-grade serous ovarian carcinoma in stage IIIC who have received neoadjuvant chemotherapy, cytoreduction with HIPEC and further chemotherapy (3 cycles) should be considered compared to cytoreduction alone after systemic chemotherapy?	IIIC	After 3 cycles of systemic chemotherapy	Cisplatin	Weak positive
COLORECTAL CANCER	In patients with colorectal carcinoma and synchronous or metachronous peritoneal carcinosis, PCI < 16, favorable biology, and good general condition, cytoreduction and HIPEC should be considered compared to systemic therapy?	IV (with peritoneal carcinomatosis)	Upfront of after 4-6 cycles of systemic chemotherapy	MMC (preferred) or platinum-based regimens*	Weak positive
GASTRIC CANCER	In patients with gastric carcinoma and only synchronous peritoneal metastasis, PCI < 6, ECOG performance status 0-1, and a therapeutic response after a first-line treatment, cytoreduction and HIPEC should be considered versus systemic chemotherapy?	IV (with peritoneal carcinomatosis)	After 4-6 cycles of systemic chemotherapy	Various*	Weak negative

Table II. *Clinical recommendations for CRS and HIPEC.*

al agents (pemetrexed and cisplatin) are extremely disappointing (median OS < 8-10 months). In a systematic review including 20 observational studies, Helm et al. analyzed a total of 1,047 patients with peritoneal mesothelioma with median PCI of 19 (25). An optimal intervention of CRS (complete cytoreduction-0/1) + HIPEC was performed in 67% of patients. Overall survival at 1, 3, and 5 years was respectively 84, 59, and 42%, being significantly higher than historical data with traditional treatment. Deraco, *et al*. reported an overall and progression-free 5-year survival of 57% and 31%, respectively, in a single-center series (26). The postoperative grade 3 morbidity was 15% in the absence of mortality correlated with the surgery, while the toxicity resulting from the chemo-hyperthermic treatment was 12%. Surgical radicality, performance status, and mitotic counts were statistically correlated with the results. In a further monocentric experience reported by Robella et al. (27), the OS at 1 and 5 years was 63% and 44%, respectively, with an overall morbidity rate of 35.7% associated with a perioperative mortality of 7.1%.

Regarding the quality of life after HIPEC CRS treatment, the potential high morbidity correlated with the complexity of the surgical procedure must be taken into account. In the experience of Piso et al. (28), even if the published data show a compromise in the postoperative quality of life at three months after surgery, there is subsequently an improvement over 6-12 months to levels higher than baseline. The evidence of the results relating to survival and quality of life despite the frequency of adverse events allowed the panel to unanimously judge a positive balance between benefits and risks deriving from the execution of CRS and HIPEC and recommended in favor of intervention.

In patients with high-grade serous carcinoma of the ovary in stage IIIC who have received neoadjuvant chemotherapy, should CRS + HIPEC and further chemotherapy (3 cycles) be considered an alternative to CRS alone after systemic chemotherapy?

The Netherlands Cancer Institute conducted a large, randomized, open-label phase III study by Van Driel et al. Their results were published in the New England Journal of Medicine in January 2018 (29). The trial was conducted on 245 patients with stage III serous ovarian cancer and included, after three courses of neoadjuvant chemotherapy with carboplatin and paclitaxel, a 1: 1 randomization with CRS only (n = 123 patients) versus CRS plus HIPEC with Cisplatin 100 mg/m2 alone (n = 122 patients). Subsequently, adjuvant treatment with systemic chemotherapy was delivered in both groups for three cycles with carboplatin and paclitaxel. The primary endpoint was relapse-free survival (RFS). The median RFS was 10.7 months in the surgery-only group versus 14.2 months in the CRS plus HIPEC group. At a median follow-up of 4.7 years, mortality was higher in the CRS group (62% of patients) than in the CRS and HIPEC group (50% of patients) (hazard ratio, 0.67; 95% CI, 0.48 to 0.94; p = 0.02). The median survival, secondary endpoint, was higher in the experimental CRS plus HIPEC group (45.7 months) than in the CRS alone group (39.9 months). The percentage of grade 3-4 adverse events reported in the two groups was almost overlapping, respectively 25% in the CRS group and 27% in the CRS plus HIPEC group (p = 0.76), supporting the feasibility and tolerability of the integrated procedure.

In consideration of the available data, AIOM judged favorable the balance between risks and benefits and provided a positive recommendation for the execution of CRS associated with HIPEC and subsequent systemic chemotherapy (3 cycles) after disease control with neoadjuvant chemotherapy in patients with high-grade, stage III, serous ovarian carcinoma. However, in patients eligible for this approach, such treatment should be carried out at high-volume centers where high expertise is expected.

Should CRS and HIPEC be considered the only alternative treatment to systemic therapy in patients with colorectal carcinoma and synchronous or metachronous peritoneal carcinosis, PCI < 16, favorable biology, and good general condition?

In a small open-label randomized Swedish study by Cashin et al. published in the European Journal of Cancer in 2016 and closed prematurely for poor accrual, 48 patients were randomized to receive CRS plus HIPEC with 5-FU versus oxaliplatin-based chemotherapy alone (30). Median survival was 25 *vs*. 18 months in favor of the experimental arm (RR 0.79, 95% CI 0.64-0.97) with a 21% reduction in the absolute risk of death. However, the progression-free survival (PFS) was lower in magnitude (RR 0.83, 95% CI 0.7-1). Against these efficacy data, no fatal events occurred at 30 days (strong evidence). 12 serious adverse events were reported in 10 patients in the experimental arm, compared with 14 grade 3-4 events reported in 12 patients in the

chemotherapy arm, with overall low evidence of consistency of the toxicity.

For this reason, the panel unanimously judged favorable the balance between risks and benefits deriving from the execution of CRS and HIPEC in peritoneal carcinosis from synchronous or metachronous colorectal carcinoma PCI < 16, favorable biology and good general conditions and provide a weak positive recommendation in favor of intervention.

Should CRS plus HIPEC versus systemic chemotherapy be used for patients with gastric carcinoma and only synchronous peritoneal metastasis, PCI < 6, ECOG performance status 0-1, and a therapeutic response after a first-line treatment?

Peritoneal carcinomatosis of gastric origin is recognized as an independent poor prognostic factor associated with poor prognosis. Systemic chemotherapy options do not differ from those of metastatic disease, although carcinosis is a factor associated with poor response to systemic treatment, mainly due to poor bioavailability of drugs on the peritoneal surface. According to the current state of evidence and literature data, although it represents a field of research in high-volume centers, the locoregional treatment with CRS and HIPEC in gastric adenocarcinoma with peritoneal carcinomatosis does not seem to represent a recommended treatment at least in the Western population. Although one randomized study (31) demonstrates a non-significant trend in favor of higher five years OS, the confidence intervals are broad and similar results are also reported for PFS. The panel, therefore, believes that the expected desirable effects (prolongation of OS and RFS / PFS) resulting from the integrated treatment of CRS and HIPEC in the PS 0-1 patient with peritoneal carcinosis alone from primary gastric cancer and a PCI < 6, are negligible and so provide strong negative recommendation against it.

CONFLICT OF INTERESTS

The authors have declared no conflict of interests.

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