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Guidelines for Perioperative Care in Cytoreductive Surgery (CRS) with or without hyperthermic IntraPEritoneal chemotherapy (HIPEC): Enhanced recovery after surgery (ERAS®) Society Recommendations — Part I: Preoperative and intraoperative management

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ABSTRACT

Background: Enhanced recovery after surgery (ERAS) pathways have been shown to considerably reduce complications, length of stay and costs after most of surgical procedures by standardised application of best evidence-based perioperative care. The aim was to elaborate dedicated recommendations for

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Abbreviations: ERAS, Enhanced recovery after surgery; CRS, Cytoreductive surgery; HIPEC, Hyperthermic intraperitoneal chemotherapy; GRADE, Grading of recommendations, assessment, development and evaluation; PICO, Population, Intervention, Comparator and Outcome.

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cytoreductive surgery (CRS) ± hyperthermic intraperitoneal chemotherapy (HIPEC) in a two-part series of guidelines based on expert consensus. The present part I of the guidelines highlights preoperative and intraoperative management.

Methods: The core group assembled a multidisciplinary panel of 24 experts involved in peritoneal surface malignancy surgery representing the fields of general surgery (n = 12), gynaecological surgery (n = 6), and anaesthesia (n = 6). Experts systematically reviewed and summarized the available evidence on 72 identified perioperative care items, following the GRADE (grading of recommendations, assessment, development, evaluation) system. Final consensus (defined as ≥50%, or ≥70% of weak/strong recommendations combined) was reached by a standardised 2-round Delphi process, regarding the strength of recommendations.

Results: Response rates were 100% for both Delphi rounds. Quality of evidence was evaluated high, moderate low and very low, for 15 (21%), 26 (36%), 29 (40%) and 2 items, respectively. Consensus was reached for 71/72(98.6%) items. Strong recommendations were defined for 37 items, No consensus could be reached regarding the preemptive use of fresh frozen plasma.

Conclusion: The present ERAS recommendations for CRS±HIPEC are based on a standardised expert consensus process providing clinicians with valuable guidance. There is an urgent need to produce high quality studies for CRS±HIPEC and to prospectively evaluate recommendations in clinical practice.

Introduction

Enhanced recovery after surgery (ERAS) pathways aim to standardise and optimise perioperative care, and hence, modulate an exaggerated postoperative metabolic and inflammatory response that is linked with adverse outcomes after major surgery [1]. The utilization of ERAS pathways combined with high degree of compliance has been shown to considerably decrease complications, length of hospital stay and costs. First demonstrated in colonic resection, ERAS protocols have since been applied to multiple types of digestive and other major surgical procedures with similar reproducible benefits [2,3]. Due to increasing demand, dedicated ERAS guidelines have been issued and updated for multiple surgical subspecialties [4–6] and recommendations have been recently published to standardise and optimise the process and methodology of guideline development [7].

Cytoreductive surgery with or without the addition of hyperthermic intraperitoneal chemotherapy (CRS±HIPEC) has become a treatment standard for various subsets of peritoneal surface malignancies [8]. These extended procedures may cause excessive tissue trauma with subsequent inflammation that ultimately lead to potentially life-threatening side effects. Major complication rates have been reported to be as high as 51% [9], and advanced resuscitation and dedicated care protocols are warranted. Early reversal of this pathophysiological cascade by improvements of perioperative care is intriguing and forms the basis of ERAS interventions. Changing historical perioperative practice related to complex procedures, however, may involve risk especially when evidence is limited.

The aim of this multidisciplinary effort was to develop ERAS guidelines for CRS±HIPEC by structured review of the most recent evidence and by use of a standardised Delphi approach and GRADE system for the definition of the quality of evidence and the strength of recommendations. A two-part series of guidelines was created based on the consensus of an expert panel. The present part I of the guidelines highlights preoperative and intraoperative management. Part II expands upon postoperative management and special considerations.

Methods

The process for ERAS guidelines for CRS±HIPEC was initiated in May 2019 but was planned in line with the recommendations for ERAS guidelines published in late 2019. The following briefly summarises the essential components, which are consistent with the standardised process for ERAS Guidelines [7]:

Forming the guideline core group, definition of timeline

The 5 members of the core group (MH, SK, LV, JV, GN) were selected for having at least 2 of the following qualifications: being clinical specialists in the field of CRS±HIPEC (n = 5), ERAS experts (n = 3) or for their expertise/track record in guideline development (n = 4). A detailed timeline was elaborated to achieve completion of the guidelines within a 12-month period of time.

Defining topics, items and delphi questions

The core group defined the topics and identified individual items reflecting the essentials for pre-, intra- and postoperative care for CRS±HIPEC. This list included traditional ERAS items from previous relevant guidelines for other surgical procedures but also procedure-specific topics, which were added by the core group (Table 1). Finally, clinical questions were formulated for every perioperative care item: 21 for 9 topics in the preoperative phase, 23 for 8 topics in the intraoperative phase and 28 for 11 topics in the postoperative phase (overall 28 topics and 72 individual items).

Assembling expert panel

Prominent active clinicians who are experts in the fields of general or gastrointestinal (GI) surgery (n = 12), gynaecologic oncology (n = 6) or anaesthesiology (m = 6) and who are also experts in peritoneal surface malignancies were invited to contribute to this guideline process and join the expert panel. Choice of experts was also guided by the endeavor to represent different countries/continents and garner well-balanced participation of different professionals, with female representation, from diverse disciplines.

Systematic review and grading of the evidence

Each expert was asked to work with another expert on 2–3 items. The goal was to systematically review and succinctly summarise the evidence for the different items related to each topic. Each item served as the basis to frame the clinical question using the PICO (population, intervention, comparator, outcome) framework. These questions successively were submitted to the expert

Table 1
List of ERAS care items: Pre- and intraoperative.

I Preoperative phase	II Intraoperative phase
1. Preadmission information, education and counselling	10. Antimicrobial prophylaxis and skin preparation
2. Preoperative optimisation: alcohol, smoking, anemia	A Preoperative antimicrobial prophylaxis
A Intensive alcohol cessation program	B Skin preparation by chlorhexidine
B Intensive behavioral intervention for smokers	C Additional SSI prevention measures
C Preoperative anemia screening and treatment	D Postoperative antibiotic prophylaxis
3. Physical exercise/prehabilitation	11. Standard anaesthetic protocol
4. Nutritional care: Screening, supplementation (oral, enteral, parenteral), immunonutrition	A Rapid sequence intubation
A Preoperative nutritional screening	B Epidural analgesia
B Nutritional/Protein supplementation	C Multimodal analgesia
C Oral immunonutrition	D Protective mechanical ventilation
5. Preoperative anaesthetic assessment	E Cardiac output monitoring
A Assessment of cardiac risk	F Use of neuromuscular antagonists
B Screening for obstructive sleep apnea	12. Intraoperative normothermia
C Complete laboratory testing	A Prevention of hypothermia
D Frailty screening	B Prevention of hyperthermia
6. Post-Operative Nausea and Vomiting (PONV)	13. Intraoperative normoglycemia
A Use of antiemetic drugs	14. Perioperative fluid management
B Total-intravenous anaesthesia	A Advanced monitoring to guide fluid therapy and catecholamines
7. Pre-anaesthetic medication	B Use of crystalloids
A Preoperative multimodal analgesia	C Limiting postoperative fluid-related weight gain
B Preoperative use of sedative/anxiolytics	15. Transfusion and management of coagulopathy
8. Preoperative bowel preparation	A Restrictive Blood transfusion policy
A CRS and HIPEC including probable colectomy	B Preemptive use of Fresh Frozen Plasma (FFP)
B CRS and HIPEC including probable rectal resection	C Tranexamic acid (TXA)
C Oral antibiotic decontamination	D Prothrombin Complex Concentrate (PCC)
9. Preoperative fasting and carbohydrate treatment	16. Abdominal and thoracic drains
A Short preoperative fasting	A Abdominal drains
B Carbohydrate loading	B Thoracic drains
	17. Early extubation

panel to evaluate using the Delphi technique. The two experts assigned to each topic were asked in addition to apply the GRADE (grading of recommendations, assessment, development, evaluation) system (i) to assess the quality of underlying evidence (very low, low, moderate, high) and (ii) to propose the strength of recommendation (weak, strong). The evidence was carefully established after a systematic discussion involving the experts and members of the core group. The level of evidence was modulated according to risk of bias, imprecision, inconsistency, indirectness, and publication bias. Of note, level of evidence was not successively submitted to the panelists for voting due to its objective nature.

Text and references for each topic were then scrutinised independently by three members of the core group in order to verify content and references, to avoid redundancy and enhance consistency between the sections, and to edit the chapter in a uniform format according to the predefined requirements.

The final version for the manuscript was modified and approved together with the two experts for each section.

Obtaining consensus by 2-round delphi process

Text sections were presented to the entire expert panel (n = 24) together with interactive links to key references in the form of an online survey (SurveyMonkey Inc., San Mateo, CA). Each section ended with one or several closed-end questions to suggest a recommendation for a given care item on a two-sided scale (strong positive, weak positive, weak negative, strong negative). Results of the 1st Delphi round were provided to the expert panel for the 2nd round. Three weeks were given for completion of each round and every participant received at least three reminders.

Consensus was defined as ≥50% of agreement for any of the four mentioned responses, or 2) those items in which 70% panelists voted on weak or strong recommendations, regardless of the direction (negative or positive).

Statistics and presentation of results

Descriptive statistics were used to summarise the results of the expert consensus. Figure presentation was preferred to allow for succinct and transparent presentation of the recommendations.

Results

Response rates for both Delphi rounds were 100%. Consensus was reached for 65 out of 72 care items in the 1st round (90.3%) and for 71 out of 72 care items in the 2nd round (98.6%). The clinical care items for pre-, intra- and postoperative phases are presented together with the experts' voting in Fig. 1A–C.

The available evidence for all 72 care items was systematically searched, discussed and presented to all panelists. Quality of evidence was estimated to be high, moderate, low and very low respectively, for 15, 26, 29, and 2 items. Specific evidence for the field of CRS±HIPEC was scarce or nonexistent for most clinical questions. In other words, indirectness was present in great majority of items (64/72) and downgraded the evidence in 37 out of 64 items.

The following paragraphs summarise the resulting recommendations together with degree of consensus and grading of evidence. In summary, over half of recommendations (n = 37) were strong positive, while the remainder were either weak positive (n = 23) or weak negative (n = 11). There was no strong negative recommendation. Consensus was not reached in only one item after two Delphi rounds, specifically the preemptive use of fresh frozen plasma (low quality of evidence). While high quality of evidence resulted mostly (14/15) in strong recommendations, weak recommendations prevailed for items with moderate (15/26), low (17/29), and very low (1/2) quality of evidence. The panelists consensually delivered strong positive recommendations, even if the evidence was low, in 12 items. On the other hand, the recommendation was weak positive despite high evidence in 1 item (Table 2).

The following section details the explicit recommendations for *preoperative and intraoperative care items* along with grade of evidence and strength of consensus (% of expert votes) (Table 3).

Preoperative phase

Preadmission information, education and counselling

Cytoreductive surgery with or without HIPEC (CRS±HIPEC) is one of the most complex, high-risk, abdominal surgeries offered for patients with advanced cancer. Decision-making around whether to proceed with CRS±HIPEC is often challenging for both patients and providers. Despite low quality of evidence, ERAS protocols for major cancer and/or abdominal surgeries have strongly recommended pre-operative counselling as a means to decrease anxiety, improve pain control and increase patient satisfaction [4,6,10,11]. A recent review has suggested that psychological prehabilitation prior to cancer surgery has the potential to improve patient-reported outcome measures, such as quality of life, somatic symptoms and psychological outcomes [12].

While the optimal form of preoperative counselling for CRS±HIPEC has not been determined, a recent study showed that patients preparing for CRS±HIPEC overwhelmingly requested audiovisual or mixed-type educational information, related to preoperative decision-making and the recovery process, as opposed to just written materials. The study also found that including caregivers as key members of the recovery process within the preoperative counselling programme is essential [13].

Summary and recommendation: Before CRS±HIPEC, preoperative counselling, ideally by mixed-type educational information should be indicated routinely to improve quality of life, somatic symptoms and psychological outcomes.

Evidence level: Low.

Recommendation strength: Strong positive (95.8% agreement, consensus reached)

Preoperative optimisation: alcohol, smoking and anaemia

Moderate to heavy consumption of alcohol is associated with weakening of the immune system, cardiovascular events, infections, bleeding complications and impaired recovery as well as alcohol withdrawal in the postoperative period. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) in the United States defines a "standard drink" as 14 gm of ethanol (5 ounces of wine, 12 ounces of 5% alcohol beer, of 1.5 ounces of 80 proof spirit). "At-risk" or "heavy drinking" is defined as 4 drinks on any day or 14 per week for men and 3 drinks on any day or 7 per week for women. In a meta-analysis, patients who were high alcohol consumers (defined as 36 gm/day for men and 24 gm/day for women based on Danish guidelines for sensible drinking) were at increased risk for postoperative morbidity, general infections, wound complications, pulmonary complications, prolonged hospital length of stay, and admission to the intensive care unit [14]. A Cochrane Review assessed the evidence of 3 randomised controlled trials (RTCs) examining the effects of alcohol cessation interventions on postoperative complications in patients who were "risky drinkers." "Risky" alcohol consumption was defined as 3 alcoholic units (3 small glasses of wine) per day or 21 units per week. This systematic review found a decrease in occurrences of postoperative complications in the groups offered intensive alcohol cessation intervention for 4–8 weeks prior to orthopedic and colorectal surgery [15].

Cigarette smoking is a risk factor for cardiovascular disease, neurologic disease, pulmonary disease, and cancer. Smoking is associated with increased morbidity, including wound complications, infections, pulmonary complications and admission to the intensive care unit [16]. Cessation of smoking has been associated with risk reduction of pulmonary, cardiovascular and wound-related complications [17]. Optimal timing for smoking cessation is unknown, but most studies demonstrate that patients should be advised to stop smoking as soon as possible, with no harm noted for short duration abstinence, and that longer periods of cessation are associated with decreased complications [18].

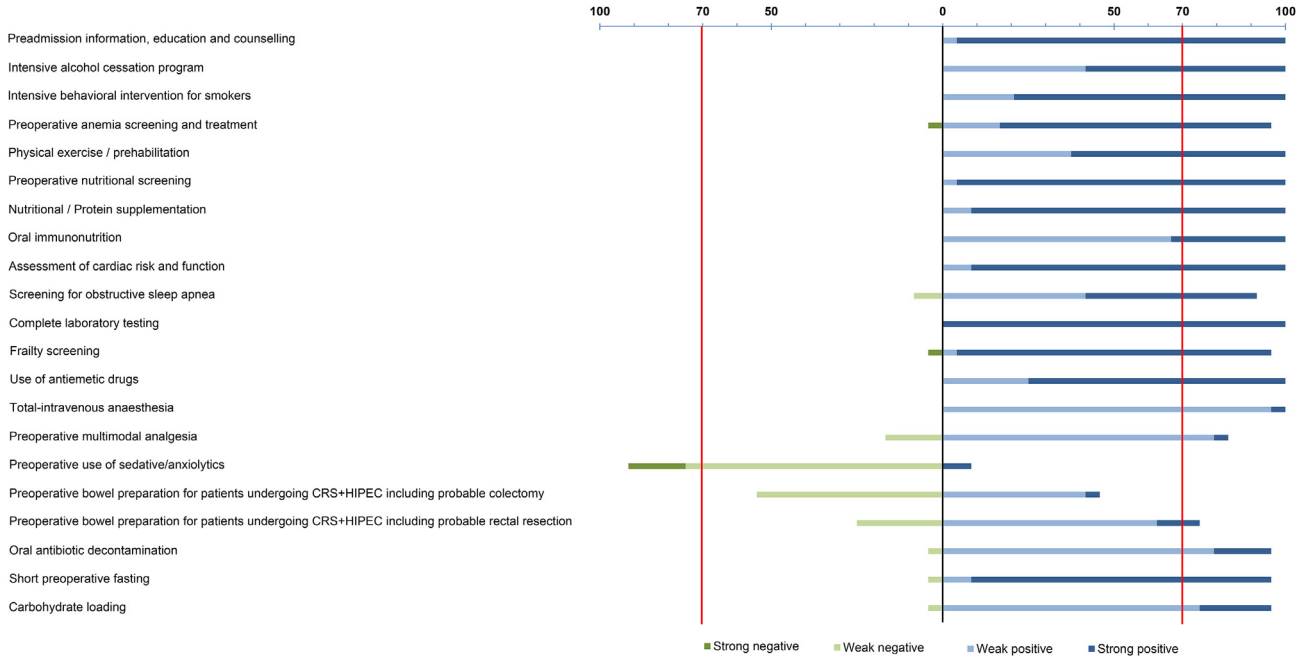

Fig. 1. Experts' voting for perioperative care items and clinical questions.

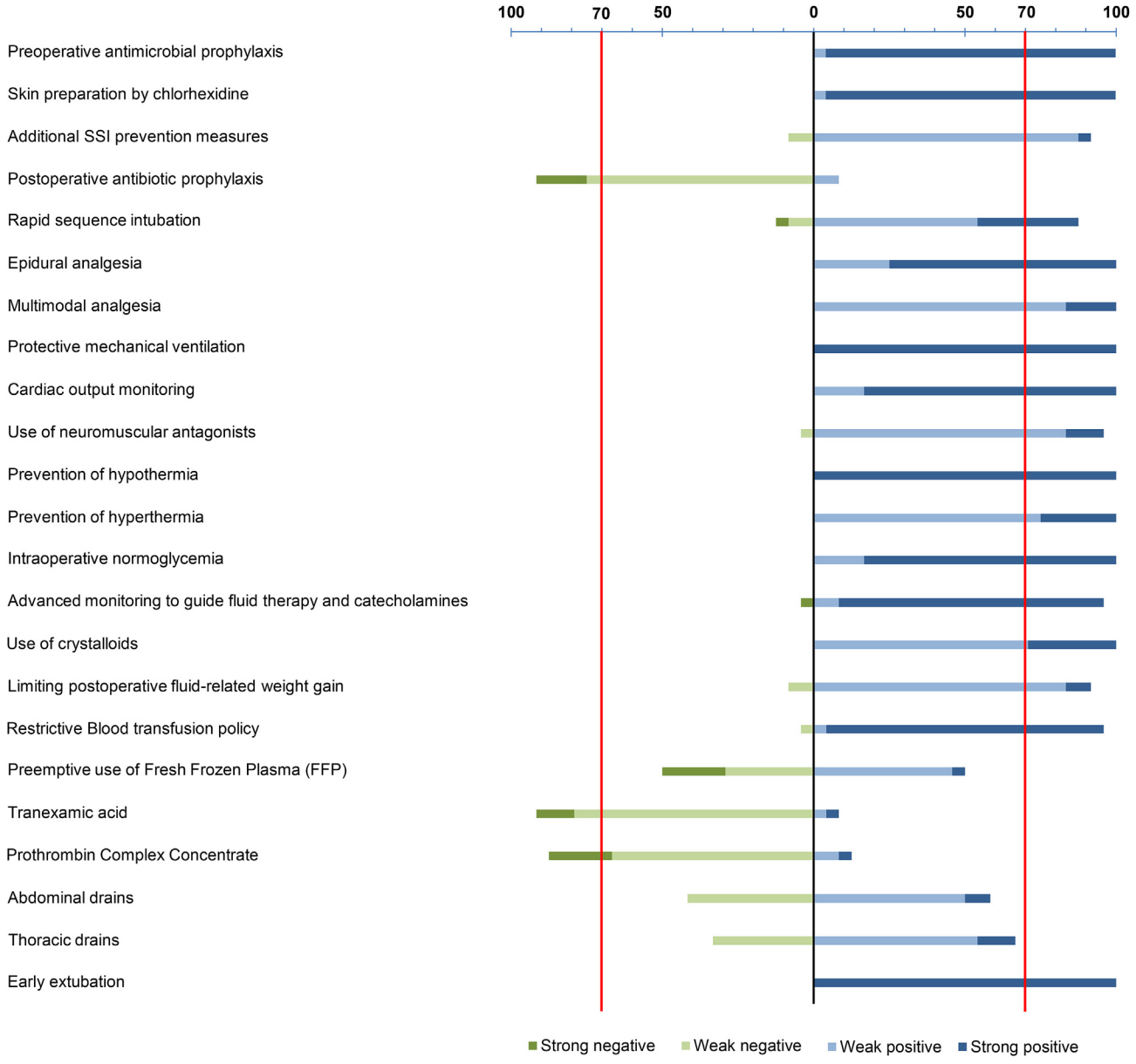

Fig. 1. (*continued*).

Behavioural support and nicotine replacement therapy are mainstays of smoking cessation interventions. One meta-analysis concluded that the treatment effect of 4 weeks of smoking cessation had significantly larger treatment effect than shorter trials [19]. Another meta-analysis concluded that cessation at 8 weeks was associated with even fewer respiratory complications than cessation at or less than 4 weeks. At least 4 weeks of abstinence was required to demonstrate reduction in respiratory complications, and at least 3–4 weeks was required for reduction in wound-healing complications. A Cochrane Review demonstrated that preoperative smoking interventions may reduce postoperative complications and that interventions beginning at 4–8 weeks prior to surgery that include weekly counselling and nicotine replacement therapy are more likely to impact postoperative complications and have a long-term effect on abstinence [20].

Alcohol and smoking cessation can be combined in a comprehensive multimodal prehabilitation programme designed to improve functional capacity and reduce postoperative complications, which may also include exercise, nutritional counselling, and anxiety reduction [21,22]. Prehabilitation is discussed elsewhere in this article.

Table 2
Strength of recommendations according to the level of evidence (Grade system).

	Level of evidence				Total
Strength of recommendation	High	Moderate	Low	Very low	
Strong positive	14	11	12	0	**37**
Weak positive	1	10	11	1	**23**
Weak negative	0	5	6	1	**12**
Strong negative	0	0	0	0	**0**
Total	**15**	**26**	**29**	**2**	**72**

Anaemia is a common finding in up to 1/3 of preoperative patients and may be due to a variety of causes (iron, folate or vitamin B12 deficiency or chronic renal insufficiency) [23]. The World

Table 3
Preoperative and Intraoperative ERAS Recommendations for Cytoreductive Surgery (CRS) with or without Hyperthermic IntraPEritoneal Chemotherapy (HIPEC): Pre- and intraoperative items.

Item	Recommendation	Evidence Level	Recommendation Strength
Preoperative phase			
Preoperative information educationand counselling	Preoperative counselling should be indicated routinely	Low	Strong positive
Preoperative optimisation	Smoking and alcohol cessation (alcohol abusers)four weeks before surgery should be indicated routinely	Moderate by indirectness	Strong positive
	Anemia identification and correction preoperatively should be indicated routinely	Low by indirectness	Strong positive
Physical exercise/prehabilitation	Prehab programme of physical exercise should be indicated routinely	Moderate by indirectness	Strong positive
Nutritional screening,supplementation	Preop nutritional screening using a validated tool and measuring serum albumin should be indicated routinel	Low by indirectness	Strong positive
	Nutritional and protein supplementation in cases of severe malnutrition should be indicated routinely	Moderate by indirectness	Strong positive
	Oral immunonutrition could be indicated	Moderate by indirectness	Weak positive
Preoperative anaesthetic assessment	Preoperative anaesthetic assessment (including cardiac risk, obstructive sleep apnea and frailty screening)	High despite indirectness	Strong positive
PONV prevention	At least 2 antiemetic drugs should be indicated routinely to prevent PONV	Moderate by indirectness	Strong positive
	TIVA could be indicated to prevent PONV	Moderate by indirectness	Weak positive
Pre-anaesthetic medication	Preoperative multimodal analgesia (including celecoxib, pregabalin, and tramadol) could be indicated	Low for CRS±HIPEC	Weak positive
	Long-acting sedatives/anxiolytics to decrease anxiety preoperatively should not be indicated	Low for CRS±HIPEC	Weak negative
Preoperative bowel preparation	MBP alone for patients undergoing CRS±HIPEC including probable colectomy should not be indicated	Moderate by indirectness	Weak negative
	MBP alone for patients undergoing CRS±HIPEC including probable rectal resection could be indicated	Moderate by indirectness	Weak positive
	In patients undergoing CRS±HIPEC, oral antibiotic decontamination with or without preoperative MBP could be indicated	Moderate by indirectness	Weak positive
Preoperative fasting and carbohydrate treatment	Preoperative fasting of 6 h for solids and 2 h for liquids should be indicated routinely	High despite indirectness	Strong positive
	Carbohydrate loading until 2 h before induction of anaesthesia could be indicated	Moderate despite indirectness	Weak positive
Intraoperative phase			
Antimicrobial prophylaxis and skin preparation	Prophylactic antibiotics within 1 h before incision should be indicated routinely	High despite indirectness	Strong positive
	Chlorhexidine-alcohol as skin disinfectant should be indicated routinely	High despite indirectness	Strong positive
	Antiseptic shower, shaving and adhesive drapes could be indicated	Moderate by indirectness	Weak positive
	Antibiotic prophylaxis during the postoperative period should not be indicated	Low by indirectness	Weak positive
Standard anaesthetic protocol	Cricoid pressure during rapid sequence intubation could be indicated	High despite indirectness	Weak positive
	Epidural analgesia should be indicated routinely	High despite indirectness	Strong positive
	Multimodal analgesia with one or several agents could be indicated routinely	Moderate despite indirectness	Weak positive
	Protective ventilation should be indicated routinely	High despite indirectness	Strong positive
	Cardiac output monitoring should be indicated routinely	High despite indirectness	Strong positive
	Deep neuromuscular block and reversal by specific antagonists could be indicated	Low by indirectness	Weak positive
Intraoperative normothermia	Prevention of intraoperative hypothermia by use of active warming devices should be indicated routinely	High despite indirectness	Strong positive
	Prevention of intraoperative hyperthermia by active measures could be performed	Low	Weak positive
Intraoperative normoglycaemia	Diabetes screening and intraoperative glycaemic control should be indicated routinely	Moderate despite indirectness	Strong positive
Perioperative fluid management	Use of GDFT and catecholamines guided by advanced/invasive monitoring should be indicated routinely	High despite indirectness	Strong positive
	Substitution of losses (fluids and protein) by use of crystalloids could be indicated	Moderate despite indirectness	Weak positive
	Limiting postop fluid-related weight gain is advised	Moderate despite indirectness	Weak positive
Transfusion and management of coagulopathy	Restrictive transfusion should be performed routinely	Moderate by indirectness	Strong positive
	Preemptive use of fresh frozen plasma	Low by indirectness	No consensus
	TXA alone or with cryoprecipitate could be administered	Moderate by indirectness	Weak negative
	Prothrombin complex concentrate could be administered	Moderate by indirectness	Weak negative

(*continued on next page*)

Table 3 (*continued*)

Item	Recommendation	Evidence Level	Recommendation Strength
Abdominal and thoracic drains	Prophylactic abdominal drains postop could be indicated	Low for CRS±HIPEC	Weak positive
	Prophylactic thoracostomy after CRS±HIPEC with diaphragmatic peritonectomy could be indicated	Low	Weak positive
Early extubation	Early extubation should be done routinely	Low by indirectness	Strong positive

Health Organization defines anaemia as haemoglobin 12 gm/dL for women and 13 gm/dL for men. Preoperative anaemia is associated with adverse outcomes in non-cardiac surgery, including cardiac events and death [24–26]. Appropriate correction of preoperative anaemia is contingent upon identifying its aetiology and the interval of time before the intended surgical procedure. Once anaemia is identified by complete blood count, additional labs may be considered: iron studies (ferritin, iron, total iron-binding capacity, transferrin saturation), B12, folate, reticulocyte count, glomerular filtration rate (on a basic metabolic panel). Patients should be screened for anaemia at least 30 days prior to surgery to allow enough time for intervention [27]. Oral or intravenous iron should be considered for iron deficiency anaemia [28]; haemoglobin may improve by 0.5–1 gm/dL per week. In addition, referral to a gastroenterologist may be considered to rule out a source of occult malignancy unrelated to the indication for cytoreductive surgery. A low folate or vitamin B12 level is an indication for supplementation. Recombinant human erythropoietin may be considered in impaired erythropoiesis but carries the risk of perioperative thrombotic events. Rarely is preoperative blood transfusion indicated, except in cases of haemoglobinopathies such as sickle cell disease [29,30].

Intensive alcohol cessation programme

Summary and recommendation: In CRS±HIPEC patients at risk for heavy alcohol consumption, an intensive alcohol cessation programme, including pharmacological intervention ±counselling ±interviews, at least four weeks prior to surgery should be indicated routinely to reduce the risk of surgical complications.

Evidence level: Moderate by indirectness.

Recommendation strength: Strong positive (58.3% agreement, consensus reached)

Intensive behavioural intervention for smokers

Summary and recommendation: In cigarette smokers who are candidates for CRS±HIPEC, an intensive behavioural intervention associated with nicotine replacement, at least four weeks prior to surgery should be indicated routinely to reduce the risk of surgical complications.

Evidence level: Moderate by indirectness.

Recommendation strength: Strong positive (79.2% agreement, consensus reached)

Preoperative anaemia screening and treatment

Summary and recommendation: Anaemia screening at least 4 weeks prior to CRS±HIPEC, prompt medical therapy (oral/intravenous iron, folate/vitamin B12 replacement or erythropoietin treatment) and preoperative transfusions for severe refractory situations should be indicated routinely in order to reduce cardiac events and mortality.

Evidence level: Low by indirectness.

Recommendation strength: Strong positive (79.2% agreement, consensus reached)

Physical exercise/prehabilitation

Prehabilitation is a multimodal programme designed to optimise the state of the patient prior to surgery and focuses on nutrition, exercise, and psychology/anxiety. Several studies in colorectal cancer surgery have shown feasibility and improved outcomes with prehabilitation [31,32] however very little information is available in gynaecologic oncology [33].

Poor preoperative nutrition has been assessed in multiple studies and is associated with impaired postoperative outcomes [34,35]. A large systematic review of 9 trials with prehabilitation nutrition and exercise showed a reduction of hospital stay by 2 days [36].

An important point of prehabilitation is to improve physical conditioning. Several randomised trials in preoperative exercise have shown improvements in preoperative oxygen uptake, quality of life, aerobic capacity and decreased complications [37–39]. Recommended tests to determine baseline physical condition include: “Six-minute walk test” with control of cardiac frequency and oxygen saturation and shallow assessment of respiratory status (respiratory pattern, thoracometry, modified MRI and Borg dyspnea scale). Training with an inspirometer to learn the breathing exercises and objectives for the postoperative period has been suggested [40].

Psychological support provides the tools to better manage anxiety related to the cancer process and surgery [41]. A large systematic review of 15 randomized trials in non-surgical patients, showed improvement in mild-moderate dementia with cognitive stimulation [42]. One RCT in gastrointestinal surgery showed a decrease in postoperative cognitive decline with cognitive intervention [43]. A Cochrane review and meta-analysis have examined interventions for stress reduction and have found that psychological interventions may benefit postoperative pain, behavior, length of stay and poor affect, however the data remains heterogeneous [12,44–46].

Summary and recommendation: In candidates for CRS±HIPEC, a prehabilitation programme of physical exercise, preferably integrated with other interventions (nutritional or anxiety control), should be indicated routinely.

Evidence level: Moderate by indirectness.

Recommendation strength: Strong positive (62.5% agreement, consensus reached)

Nutritional care: screening, supplementation (oral, enteral, parenteral) and immunonutrition

Preoperative malnutrition has been associated with increased postoperative morbidity and mortality and poor oncological outcomes in patients with gastrointestinal cancers [47–50]. Routine preoperative nutritional screening is therefore strongly recommended (European Society for Clinical Nutrition and Metabolism [ESPEN] guidelines GI surgery 2017) [51]. Valuable screening tools include the Malnutrition Universal Screening Tool (MUST) [52], the Nutritional Risk Screening score NRS-2002 [53], the PreOperative Nutrition Score (PONS) [54]. Common criteria of all these tools include low body mass index (BMI <18.5), reduced food intake,

older age (>65 or 70, respectively), recent unintentional weight loss (>10% over 3–6 months) and low serum albumin (<30 mg/l).

Patients with malnutrition or at nutritional risk should document daily intake (diary) and benefit of oral nutritional supplements (≥7 days) containing at least 1.2–2.0 gm protein/kg per day [55]. Preferentially enteral or parenteral nutrition (in non-functioning GI tract) should be initiated in patients with severe malnutrition or if sufficient oral intake is not achievable [56,57]. Correction of malnutrition requires a minimal treatment of 7–14 days [51].

Goals of preoperative evaluation are to assess the patient's medical status and ability to tolerate anaesthesia, mitigate the risks of anaesthesia and surgery, and to prepare the patient for the procedure. The perioperative pathophysiological changes associated with CRS±HIPEC can cause major organ dysfunction. It is therefore imperative to perform a detailed and thorough preoperative evaluation as soon as this surgical procedure is considered [58–60].

Preoperative nutritional screening

Summary and recommendation: In CRS±HIPEC patients, preoperative nutritional screening by use of a validated tool and by measuring serum albumin should be indicated routinely.

Evidence level: Low by indirectness.

Recommendation strength: Strong positive (95.8% agreement, consensus reached)

Nutritional/protein supplementation

Summary and recommendation: In patients with malnutrition or at risk for malnutrition, nutritional and protein (>1.2 g/kg/day) supplementation (oral>enteral>parenteral) for at least 5 days and up to 14 days in cases of severe malnutrition should be indicated routinely.

Evidence level: Moderate by indirectness.

Recommendation strength: Strong positive (91.7% agreement, consensus reached)

Oral immunonutrition

Summary and recommendation: Oral immunonutrition for 5–7 days prior to CRS±HIPEC could be indicated in an attempt to reduce postoperative (infectious) complications.

Evidence level: Moderate by indirectness.

Recommendation strength: Weak positive (66.7% agreement, consensus reached)

Preoperative anaesthetic assessment

Goals of preoperative evaluation are to assess the patient's medical status and ability to tolerate anaesthesia, mitigate the risks of anaesthesia and surgery, and to prepare the patient for the procedure. The perioperative pathophysiological changes associated with CRS±HIPEC can cause major organ dysfunction. It is therefore imperative to perform a detailed and thorough preoperative evaluation as soon as this surgical procedure is considered [58–60].

The Revised Cardiac Risk Index and American College of Surgeons National Surgery Quality Improvement Program (ACS NSQIP) surgical risk calculator (https://riskcalculator.facs.org/RiskCalculator/) are useful for stratification of perioperative cardiac risk and provide a complementary prognostic value that can help clinicians in their decision-making process [58]. Patients with reduced cardiac reserve and those with a previous history of heart failure or chemotherapy-induced cardiotoxicity may require echocardiogram and stress testing during the preoperative assessment.

Ascites that is often associated with peritoneal carcinomatosis can result in basal atelectasis which places these patients at risk of perioperative hypoxia. The STOP-BANG (Snoring, Tiredness, Observed apnea, blood Pressure, Body mass index, Age, Neck circumference and Gender) score for obstructive sleep apnea (OSA) should also be calculated to anticipate a need for perioperative respiratory support such as continuous positive airway pressure (CPAP). In patients previously diagnosed with OSA, it is important to document the settings of positive airway pressure device used at home and to use CPAP preoperatively to reduce hypoxic events [58,61].

Laboratory tests should include complete blood count, metabolic panel, and coagulation studies. Glomerular filtration rate (GFR) should be calculated as it has been shown to be a sensitive and reliable predictor of in-hospital mortality and morbidity [62].

Frailty has been defined as a state of increased vulnerability and poor resolution of homeostasis after physiological stress. Frailty is also associated with worse outcomes after major surgery. The clinical frailty scale (CFS) is a global assessment that uses a nine-level scale that grades the patient's overall condition from fit to terminally ill [63]. The CFS has been shown to independently predict readmission, disability, and death [64,65]. Patients with frailty score greater than 4, unless modifiable, may not be candidates for CRS±HIPEC.

The Ovarian Consensus Panel considered the following as relative contraindications for CRS±HIPEC: heart failure (94%), pulmonary compromise (94%), previous pulmonary embolus 63%. This is not a definitive list and every case should be individualized [66,67].

Assessment of cardiac risk and function

Summary and recommendation: Preoperative anaesthetic work-up before CRS±HIPEC including *assessment of cardiac risk and function* should be indicated routinely.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (91.7% agreement, consensus reached)

Screening for obstructive sleep apnea

Summary and recommendation: Preoperative anaesthetic work-up before CRS±HIPEC including *screening for obstructive sleep apnea* should be indicated routinely.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (50.0% agreement, consensus reached)

Complete laboratory testing

Summary and recommendation: Preoperative anaesthetic work-up before CRS±HIPEC including *complete laboratory testing* (complete blood count, metabolic panel, renal function, coagulation tests) should be indicated routinely.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (100.0% agreement, consensus reached)

Frailty screening

Summary and recommendation: Preoperative anaesthetic work-up before CRS±HIPEC including *frailty screening* should be indicated routinely.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (91.7% agreement, consensus reached)

Post-operative nausea and vomiting (PONV)

Post-operative nausea and vomiting (PONV) is common after

CRS±HIPEC. The aetiology of PONV can be classified into patient factors, anaesthetic factors and surgical factors. While the systemic uptake of chemotherapeutic agent during HIPEC is limited, chemotherapeutic agents often have an emetogenic effect (40–50% of nausea and vomiting) [68].

The incidence of PONV is reported to be approximately 25–35% of all surgical patients, but the incidence varies depending on the type of surgery [69]. The incidence of PONV can be significantly reduced with a multifactorial, multimodal approach [70,71]. Most PONV guidelines advocate risk stratification using well validated PONV scoring systems. These scoring systems classify patients into low, medium and high risk groups and allow individual tailoring of perioperative PONV prophylaxis [72].

Modifiable factors that are associated with an increased risk of PONV include opiate analgesics, nitrous oxide and inhalational anaesthesia [69,73]. Thoracic epidural or alternative regional anaesthetic technique can significantly reduce the incidence of PONV. The use of total intravenous anaesthesia has been shown to reduce the incidence of PONV in high risk groups when compared with inhalational anaesthesia, although this only seems to be true for the early post-operative phase [74].

Many antiemetic medications are available, targeting different receptors. There is strong evidence confirming an enhanced anti-emetic effect with the use of $\geq$2 anti-emetics with different mechanisms of action [75]. There is no recognized best combination of specific anti-emetic agents.

Use of antiemetic drugs

Summary and recommendation: In CRS±HIPEC candidates, a combination of at least 2 antiemetic drugs (ondansetron, dexamethasone, droperidol), should be indicated routinely to prevent PONV.

Evidence level: Moderate by directness.

Recommendation strength: Strong positive (75.0% agreement, consensus reached)

Total intravenous anaesthesia

Summary and recommendation: In CRS±HIPEC candidates, total intravenous anaesthesia as an alternative to inhalation anaesthesia, could be indicated to prevent PONV.

Evidence level: Moderate by directness.

Recommendation strength: Weak positive (95.8% agreement, consensus reached)

Pre-anaesthetic medication

Preoperative medications include multimodal pain medications and anxiolytics. Only one retrospective study has studied use of multimodal analgesia in 373 patients undergoing CRS with a combination of celecoxib 200–400 mg, pregabalin 75 mg and tramadol 100 mg [76]. These medications in combination with intraoperative non-opioid analgesia like lidocaine infusions, ketamine and dexmedetomidine, reduced postoperative opioid consumption by almost 90% and length of hospital stay by 4–5 days. Reduced opioid consumption is likely to lead to improved bowel function and motility, leading to reduced length of stay, but was not associated with improved survival rates [76].

Preoperative anxiety may have a huge effect on the patient's personal experience and postoperative pain [77]. Classic pre-anaesthetic medication with anxiolytics is not encouraged. According to a randomized study, patients undergoing elective surgery under general anaesthesia, sedative premedication with lorazepam compared with placebo or no premedication did not improve the self-reported patient experience the day after surgery, but was associated with prolonged time to extubation and a lower rate of early cognitive recovery [78]. Moreover, in other studies, premedication was associated with delays of oral resumption of liquids eliciting adverse effects in terms of optimal perioperative care [79].

In the operative room, anxiolytics or opioids are often administered to increase patient's comfort during the performance of venous cannulation or aid performing regional anaesthesia. Long-acting medications should be avoided as they defer postoperative recovery and have been linked to psychomotor disability, reduced mobilisation, and late refeeding. Short-acting drugs such as midazolam (0.04 mg/kg) are a better option. However, even midazolam has shown residual effects during longer evaluation time frames, and clinically, it has been associated to late discharge from the post-anaesthesia care unit and lower scores on psychomotor function, especially in older patients [80–82].

Preoperative multimodal analgesia

Summary and recommendation: Preoperative multimodal analgesia including celecoxib 200–400 mg, pregabalin 75 mg and tramadol 100 mg could be indicated to reduce postoperative opioid consumption, resumption of bowel function, and length of stay.

Evidence level: Low for CRS±HIPEC.

Recommendation strength: Weak positive (79.2% agreement, consensus reached)

Preoperative use of sedative/anxiolytics

Summary and recommendation: Considering the potential postoperative effects in terms of early cognitive recovery, time to extubation, time to discharge from the post anaesthesia care unit, refeeding, and mobilisation, the use of long-acting sedatives/anxiolytics before CRS±HIPEC to decrease anxiety should not be indicated (75.00% weak negative).

Evidence level: Low for CRS±HIPEC.

Recommendation strength: Weak negative (75.0% agreement, consensus reached)

Preoperative bowel preparation

For many years preoperative mechanical bowel preparation (MBP) was used with the assumption that this intervention decreased rates of infection and anastomotic leaks. Despite the perceived advantage, patients experienced discomfort, dehydration, electrolyte abnormalities and prolonged hospital admissions. Within the patient population undergoing peritoneal stripping and HIPEC, this becomes particularly important given that this group of patients will often have multiple bowel resections, anastomoses and pelvic *en-bloc* resections.

Currently, there is a lack of high-level investigations examining bowel preparation within the CRS±HIPEC population, and therefore evidence must be derived from the colorectal literature, which has remained controversial. Multiple studies and meta-analyses have shown that the use of MBP alone is not associated with a decrease in overall mortality, surgical site infection (SSI) rate, anastomotic leak rate or reoperation compared to no MBP [83–86]. Retrospective studies have re-opened the debate on preoperative use of oral antibiotics (OAB) with a potential decrease in hospital length of stay, SSI and readmissions after colorectal surgery [87,88]. Several meta-analyses of randomised controlled trials have since examined the role of OAB. Chen et al. [89] showed that a combination of MBP+OAB was associated with a lower rate of SSI overall (7.2 vs. 16%, $P < 0.001$) and incisional SSI (4.6% vs. 12.1%, $P < 0.001$) when compared to MBP with intravenous antibiotics (IVA). Similarly, McSorely et al. [90] examined 22 studies with 57207 patients, and found that MBP+OAB+IVA were better than MB+IVA (Or0.45 CI 0.34–0.59). Toh et al. [91] reviewed 38 randomized trials and

showed that MBP+OAB had a lower rate of SSI compared to MBP alone (OR 0.7 CI 0.57–0.88); MBP alone was equivalent to no preparation and MBP+OAB was equivalent to OAB alone. The most recent Cochrane review on antibiotic prophylaxis also supports antibiotic use, both OAB and IVA, but finds this may increase the risk of Clostridium difficile [92]. The American College of Surgeons and Surgical Infection Society recommend using the combination of MBP+OAB [93].

Several retrospective trials have examined OAB versus MBP+OAB. These studies found no difference in outcomes for the two groups with respect to infectious morbidity, anastomotic leak, readmission or hospital stay [94–96]. These studies suggest that OAB is the crucial element in preoperative bowel preparation. This is further supported by the recent publication of the MOBILE (Mechanical and oral antibiotic bowel preparation versus no bowel preparation for elective colectomy) study in 2019, which compared MBP+OAB to no preparation [97]. This multicentre single blind trial showed no difference between SSI, anastomotic dehiscence or reoperation rate between rates. Several current RCTs are registered with clinicaltrials.gov that will be comparing OAB versus MBP+OAB including MECCA (#NCT03563586) and COLONPREP (#NCT03475680).

For patients undergoing CRS±HIPEC including probable colectomy

Summary and recommendation: Preoperative mechanical bowel preparation alone for patients undergoing CRS±HIPEC including probable colectomy should not be indicated to reduce the incidence of surgical site infection, and anastomostic leak.

Evidence level: Moderate by indirectness.

Recommendation strength: Weak negative (54.2%)

For patients undergoing CRS±HIPEC including probable rectal resection

Summary and recommendation: Preoperative mechanical bowel preparation alone for patients undergoing CRS±HIPEC including probable rectal resection could be indicated to reduce the incidence of morbidity and infectious complications.

Evidence level: Moderate by indirectness.

Recommendation strength: Weak positive (62.5% agreement, consensus reached)

Oral antibiotic decontamination

Summary and recommendation: In patients undergoing CRS±HIPEC, oral antibiotic decontamination with or without preoperative mechanical bowel preparation could be indicated to reduce the incidence of surgical site infection, and anastomotic leak.

Evidence level: Moderate by indirectness.

Recommendation strength: Weak positive (79.2% agreement, consensus reached)

Preoperative fasting and carbohydrate treatment

Traditionally, long fasting before elective surgery was considered the norm in order to avoid full stomach and thus the risk of pulmonary aspiration [98]. Ever since, several RCTs have proven that fasting from midnight does not reduce gastric content [99]. Consecutively, numerous anaesthesia societies recommended to allow a light meal up to 6 h and non-alcoholic clear fluids up to 2 h before surgery [100].

Risk factors for prolonging gastric emptying time for solids are smoking, functional dyspepsia, psychological stress, female hormones [98,101,102] but not obesity [103]. Some data show that diabetic patients with neuropathy may have delayed gastric emptying for solids but no conclusive data is available concerning fluids [104]. Patients with peritoneal metastases frequently suffer from abdominal pain, bloating, indigestion, abdominal distention or early satiety, but there is no evidence for longer gastric emptying [105–107].

Preoperative administration of oral carbohydrates (CHO: maltodextrin 12.5%, 240–285 mOsm/kg, usually in 800 mL solution) was introduced to diminish the catabolic response induced by overnight fasting and surgery [108,109]. A Cochrane review on CHO analyzed 27 trials and 1976 patients having different types of elective minor and major abdominal surgery, but also orthopaedic surgery, cardiac surgery, and thyroidectomy [110]. CHO had no significant impact on complications but induced a moderate reduction of hospital stay in patients undergoing major abdominal surgery (reduction by 1.66 days, 95% CI - 2.97 to - 0.34) when compared to the placebo or fasting group.

A more recent large RCT (PROCY) of 880 patients undergoing elective major abdominal surgery studied oral CHO administration versus placebo [109]. The RCT failed to show reduction of postoperative infections (primary end-point) but demonstrated improvement in insulin requirements and hyperglycaemia ($\geq$180 mg/dL) which is consistent with previous data [111].

Finally, several cohorts reported the use of ERAS protocols in CRS±HIPEC [112–117]. Some of these studies did not report duration of fasting or administration of CHO [112,113].

Short preoperative fasting

Summary and recommendation: Short preoperative fasting of 6 h for solids and 2 h for liquids before CRS±HIPEC should be indicated routinely.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (87.5% agreement, consensus reached))

Carbohydrate loading

Summary and recommendation: Carbohydrate loading until 2 h before induction of anaesthesia for CRS±HIPEC could be indicated to reduce postoperative insulin resistance and perioperative discomfort, including anxiety.

Evidence level: Moderate despite indirectness.

Recommendation strength: Weak positive (75% agreement, consensus reached)

Intraoperative phase

Antimicrobial prophylaxis and skin preparation

Cytoreductive surgery with or without HIPEC can be clean contaminated or contaminated surgery depending on the absence or presence of bowel resection respectively. Incidence of postoperative SSI after CRS and HIPEC ranges from 11% to 46% [118–121]. Parenteral antibiotics in the form of cephalosporins are the preferred for antimicrobial prophylaxis. Metronidazole is administered if there is involvement of bowel transaction (contaminated cases) [122,123]. Intravenous antibiotics are administered within 1 h of incision in order to obtain the highest drug serum levels at incision, and are repeated based on the pharmacokinetics of the drug [122]. Additional prophylactic antimicrobial agent doses after the surgery are not indicated in clean contaminated cases [124]. However, around 51% surgeons practice the use of postoperative antibiotic [125] despite the absence of data in the literature regarding prolonged antibiotic prophylaxis.

A prospective study has shown the reduction in rate of SSI by preoperative screening for superficial infections and directed therapy [126]. The Centres for Disease Control and Prevention (US) has recommended full body shower or bathing with soap

(antimicrobial or non-antimicrobial) at least the night before the operative day [124]. Preoperative hair removal by the use of clippers has not shown to reduce SSI [127].

Two of the most commonly used active components in preoperative skin antisepsis are chlorhexidine gluconate and povidone iodine. Chlorhexidine gluconate is the preferred agent in clean-contaminated surgery unless contraindicated [128–130]. There is no evidence for use of preoperative antiseptic shower or adhesive incise drapes [131,132].

Preoperative antimicrobial prophylaxis

Summary and recommendation: Prophylactic antibiotics within 1 h before incision for CRS±HIPEC without need for routine repeated administration should be indicated routinely to prevent surgical site infection.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (95.8% agreement, consensus reached)

Skin preparation by chlorhexidine

Summary and recommendation: Chlorhexidine-alcohol as skin disinfectant, in alternative to povidone-iodine should be indicated routinely to prevent surgical site infection.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (95.8% agreement, consensus reached)

Additional surgical site infection prevention measures

Summary and recommendation: Antiseptic shower, shaving and adhesive drapes could be indicated to prevent surgical site infection.

Evidence level: Moderate by indirectness.

Recommendation strength: Weak positive (87.5% agreement, consensus reached)

Postoperative antibiotic prophylaxis

Summary and recommendation: The antibiotic prophylaxis during the postoperative period should not be indicated to prevent surgical site infection.

Evidence level: Low by indirectness.

Recommendation strength: Weak negative (75% agreement, consensus reached)

Standard anaesthetic protocol

Anaesthesia for CRS±HIPEC is conducted using short acting anaesthetic agents (e.g. propofol 1.5–2.5 mg/kg) and neuromuscular blocking drugs (e.g. rocuronium 0.6 mg/kg). The latter should be titrated using neuromuscular monitoring; in addition, deep neuromuscular blockade may improve the surgical field during laparoscopic surgery [133], although if employed, adequate neuromuscular reversal must be confirmed prior to tracheal extubation. Maintenance of anaesthesia can be achieved either with a volatile based technique (e.g. sevoflurane or desflurane to an age-adjusted minimum alveolar concentration value of about 1.0) or total intravenous anaesthesia (TIVA) with propofol and remifentanil, using target controlled infusion pumps set to deliver approximately 3–6 mcg/mL, adjusted according to patient response and processed electroencephalographic monitoring. There is currently considerable interest as to which technique is preferable for patients undergoing major oncological resections, with some evidence supporting the use of TIVA for improved long term outcome in cancer surgeries [134] although no one anaesthetic technique to date has proven superiority for CRS±HIPEC. More recently, there is currently enthusiasm for multimodal anaesthesia, which includes agents such as dexmedetomidine, lidocaine, magnesium sulphate and ketamine to decrease perioperative opioid use with a lower risk of postoperative respiratory complications and faster return to gastrointestinal function [135–139]. Other key areas are the strategies to minimize postoperative nausea and vomiting (PONV) with multimodal antiemetic regimes, avoidance of nitrous oxide and the use of TIVA [140]. Epidural anaesthesia has the potential to provide excellent pain relief for large laparotomies [141,142] and reduce pulmonary complications [143]. Prolonged thoracic epidural analgesia (over 72 h) is currently of interest as it may contribute to both an improved disease-free survival and overall survival [144]. Analgesia is described further in Section 21 of the Guidelines for Perioperative Care in Cytoreductive Surgery (CRS) with or without Hyperthermic IntraPEritoneal Chemotherapy (HIPEC): Enhanced Recovery After Surgery (ERAS®) Society Recommendations — Part II: Postoperative Management and Special Considerations.

This patient group presents a wide range of specific physiologic challenges within the respiratory, cardiac, renal and coagulation systems. Abdominal distension from ascites will decrease the functional residual capacity of the lungs, thus increasing the likelihood of arterial oxygen desaturation with an increased PaO_2/FiO_2 ratio as well as an increased $PaCO_2$. Pulmonary adverse events are common in this group of patients [145]. A number of interventions have been described to address these, including intraoperative protective mechanical ventilation, setting appropriate levels of fraction of inspired oxygen (FiO_2) and positive end expiratory pressure (PEEP) with low tidal volumes ($\leq$8 mL/kg of predicted body weight) [146] and avoid increased driving pressures [147]. The avoidance of high intraoperative FiO_2 concentrations recommended [140]. In addition, the abdominal distension will also cause a rise in intragastric pressure predisposing to aspiration of gastric contents during the induction of anaesthesia), and thus rapid sequence intubation should be considered in this patient group.

Standard anaesthetic monitoring is recommended throughout [148]. In addition, since extensive fluid shifts occur during the cytoreductive phase, and hyperthermia leads to vasodilation and a hyperdynamic circulation with an increase in heart rate, close monitoring of central venous pressure and cardiac index during the HIPEC phase is required. Standard methods for haemodynamic monitoring of cardiac output and stroke volume variation (SVV) are recommended to guide goal directed fluid therapy [149,150] and are described further in section 14. An arterial line is an important monitor to guide vasoactive drug use and arterial blood gas sampling. The latter is important to monitor and if necessary treat metabolic sequelae such as lactic acidosis developing from the hypermetabolic state. Temperature must be monitored continuously and reliably during the whole procedure with both intraperitoneal (subdiaphragmatic and pelvic) and core temperature monitoring (e.g. esophageal, tympanic probes or a zero heat-flux technique).

In addition, close observation and management of coagulation status is recommended, both laboratory tests (e.g. INR) and point-of-care tests, such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM), as coagulopathy is common and multifactorial [151,152]. The use of tranexamic acid and cryoprecipitate has been recommended to reduce blood transfusion rate [153].

Rapid sequence intubation

Summary and recommendation: Cricoid pressure during rapid sequence intubation could be indicated to decrease risk of pulmonary aspiration in patients undergoing CRS±HIPEC.

Evidence level: High despite indirectness.

Recommendation strength: Weak positive (54.2% agreement,

consensus reached)

Epidural analgesia

Summary and recommendation: Epidural analgesia (T5-T11, low dose of local anaesthetic and opioids) for ≥72 h after CRS/HIPEC should be indicated routinely to obtain pain relief, spare opioids and hasten the resumption of bowel function.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (75% agreement, consensus reached)

Multimodal analgesia

Summary and recommendation: Multimodal analgesia with integration of one or several agents (dexmedetomidine, magnesium sulphate, lidocaine and ketamine) could be indicated.

Evidence level: Moderate despite indirectness.

Recommendation strength: Weak positive (83.3% agreement, consensus reached)

Protective mechanical ventilation

Summary and recommendation: Protective mechanical ventilation with low tidal volumes, as compared to conventional ventilation should be indicated routinely to reduce the risk of postoperative pulmonary complications.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (100.0% agreement, consensus reached)

Cardiac output monitoring

Summary and recommendation: Minimally invasive cardiac output monitoring to guide goal-directed fluid therapy should be indicated routinely to reduce postoperative complications.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (83.3% agreement, consensus reached)

Use of neuromuscular antagonists

Summary and recommendation: Deep neuromuscular block and reversal by specific antagonists could be indicated to improve surgical exposure, decrease OR time and reduce the patient's risk of residual blockade.

Evidence level: Low by indirectness.

Recommendation strength: Weak positive (83.3% agreement, consensus reached)

Intraoperative normothermia

Monitoring and maintenance of normothermia (36 °C) is a key component of fast track protocols in cytoreductive surgery [112,113]. Further, a survey with responses from 29 out of 41 centres noted active temperature monitoring usually with an esophageal temperature probe [113]. Prevention of hypothermia during cytoreductive surgery occurred usually with forced air warmers (79% of centres) and warming mattresses (41% of centres) [113]. For the HIPEC phase, 18 of 29 (62%) centres actively cooled patients using forced air blowers on cool or ambient settings. All centres allowed some increase in core temperature; range of 36–41 °C. With increased body temperature there is corresponding effects on metabolic rate including increased oxygen demand, heart rate, end tidal CO_2 levels and metabolic acidosis/increased lactate values [154]. No studies have been published correlating increased core temperature during HIPEC and postoperative morbidity.

There is a high level of evidence supporting intraoperative normothermia in elective colonic surgery and other areas including major gynecologic procedures, rectal resection, and gastric resection; all areas which may be included in cytoreductive surgical procedures with HIPEC [1]. Several meta-analyses and randomised trials have demonstrated that the prevention of hypothermia during major abdominal surgery significantly reduces wound infections, cardiac complications, venous thromboembolic events and intraoperative bleeding and transfusion need [155–158]. The majority of randomized controlled trials of enhanced recovery after surgery in colorectal surgery included prevention of hypothermia [159]. Maintenance of intraoperative normothermia to prevent postoperative complications is well accepted and further trials are unlikely to be performed in this area.

Prevention of hypothermia

Summary and recommendation: Prevention of intraoperative hypothermia (<36 °C) by use of active warming devices, by maintaining an ambient temperature of ≥21 °C, and by warming of anaesthetic gases, intravenous and irrigation fluid should be performed routinely.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (100.0% agreement, consensus reached)

Prevention of hyperthermia

Summary and recommendation: Prevention of intraoperative hyperthermia (>41 °C) by active measures (forced air blowers, cool packs and ambient settings) could be performed.

Evidence level: Low.

Recommendation strength: Weak positive (75.0% agreement, consensus reached)

Intraoperative normoglycaemia

Intraoperative glycaemic control is recommended to minimize postoperative morbidity and mortality [160]. There are several glycaemia influencing factors for patients submitted to CRS and HIPEC related both to surgery itself (surgical stress, fasting, fluid administration) and to HIPEC (hyperthermia, chemotherapy, intraperitoneal carrier used) [161].

During surgery, insulin resistance is a common event. It is a physiological response induced by surgical trauma, and a catabolic response induced by fasting. It is frequently combined with electrolyte disorders following fluid administration during surgery [162]. During HIPEC, hyperthermia can cause higher lactate levels which may lead to metabolic acidosis, also worsened by tumorolysis induced by peritoneal chemotherapy [163]. Moreover, some chemotherapeutic agents (i.e. oxaliplatin) are diluted in dextrose 5% solutions, due to their tendency to be converted in oxalate, which can cause an acute peripheral neuropathy [164].

The NICE-SUGAR study suggests keeping an intraoperative glucose target of 140–180 mg/dL, to avoid the major intraoperative risk of hypoglycaemia [165]. Indeed, avoiding perioperative hypoglycaemia is associated to a lower morbidity rate in both diabetic and non-diabetic patients [166].

Conversely, perioperative hyperglycaemia leads to a higher surgical site infection rate [167] and patients with a misdiagnosed diabetes can develop worse post-operative outcomes with respect to diabetic patients [168]. For this reason, surgical patients without diabetes but with risk factors such as age >45 and BMI >25 should be screened for hyperglycaemia and Hb1Ac levels [169].

Since CRS and HIPEC are usually performed by laparotomy due to the complexity of surgery, these patients have a higher risk to develop wound infection, especially in presence of risk factors.

All modifiable factors to preserve intraoperative normoglycaemia, including oral preoperative CHO loading, use of minimally invasive surgery when possible, thoracic epidural analgesia and

early feeding [5] should be pursued in case of CRS and HIPEC.

Summary and recommendation: Diabetes screening and intraoperative glycaemic control (target: 140–180 mg/mL) should be indicated routinely to avoid intraoperative hyper- or hypoglycaemia and to reduce postoperative complications.

Evidence level: Moderate despite indirectness.

Recommendation strength: Strong positive (83.3% agreement, consensus reached)

Perioperative fluid management

Patients following CRS and HIPEC have a capillary leak with massive loss of fluid, blood and protein [170,171] causing substantial fluid shifts. Although parameters such as arterial blood pressure and urine output have been used to guide fluid therapy in the past, more recently goal-directed therapy is a recommended approach using stroke volume optimisation [172–175]. This will minimize the risks associated with both hypovolemia (e.g. renal dysfunction) and hypervolemia (e.g. tissue edema) [170,172,176–178].

Fluid administration of 9–12 mL/kg/h has been advocated, in particular if platinum derivatives are used to ensure a satisfactory urinary output (at least 1 mL/kg/h) [152,179]. The use of furosemide, dopamine and mannitol for urinary output cannot be generally recommended [180,181].

The preferred use of either crystalloid or colloid infusions is still a matter of debate. However, the need to substitute the protein loss of up 700 gm per day is recommended [151,182,183]. Transfusion of fresh frozen plasma should be restricted to patients with coagulation perturbations as the administration is associated with an increased risk of multi-organ failure and acute respiratory distress syndrome [184]. The use of crystalloids should be done in accordance with measured haemodynamic parameters as liberal use would increase interstitial edema with negative consequences not only for all vital organs but also for intestinal anastomoses with increased risk of leakage [172,185].

During surgery, as increased inflammatory mediators are released, patients will present with vasodilation and a hyperdynamic circulatory state. This will be counterbalanced not only by fluid administration but may also require catecholamines [151,186]. During the first 24 h after surgery, patients will lose up to 10 L of fluid per day, most of it via intraabdominal drains. Therefore, there is a need to substitute this loss, mostly with crystalloids and albumin.

Great care is required to avoid excess perioperative intravenous fluids. This may lead to patients exceeding weight gain thresholds (>3.5 kg), which are associated with adverse postoperative outcomes, particularly in in open colorectal surgery [187].

Advanced monitoring to guide fluid therapy and catecholamines

Summary and recommendation: During CRS±HIPEC, use of goal-directed fluid therapy and catecholamines guided by advanced/invasive monitoring should be indicated routinely in order to maintain adequate urine output of >1 mL/kg/h.

Evidence level: High despite indirectness.

Recommendation strength: Strong positive (87.5% agreement, consensus reached)

Use of crystalloids

Summary and recommendation: During CRS±HIPEC, substitution of losses (fluids and protein) by use of crystalloids could be indicated.

Evidence level: Moderate despite indirectness.

Recommendation strength: Weak positive (70.8% agreement, consensus reached)

Limiting postoperative fluid-related weight gain

Summary and recommendation: Limiting postoperative fluid-related weight gain (target: < 3.5 kg on postoperative day 3) is advised to reduce morbidity, LOS, ICU LOS, and time to recovery of bowel function.

Evidence level: Moderate despite indirectness.

Recommendation strength: Weak positive (83.3% agreement, consensus reached)

Transfusion and management of coagulopathy

Coagulopathy may appear in 40% of patients in the perioperative period [187]. Transfusion of allogenic blood products is associated with increased morbidity and mortality with adverse effects on the prognosis due to immunosuppression [188,189].

Liberal ('10/30' approach: transfusion for haemoglobin <10 g/dL or haematocrit <30%) and restrictive (trigger of 7 g/dL in the asymptomatic patient without significant cardiac comorbidity) approaches for blood transfusion are common [189]. A meta-analysis has demonstrated that the restrictive strategy was non-inferior to the liberal strategy with respect to 30-day mortality and morbidity (pulmonary, infectious, renal, and cardiovascular) [190]. A Cochrane Review of 31 trials involving 12,587 patients across multiple specialties provides good evidence that transfusions with allogenic packed red blood cells can be avoided in most patients with haemoglobin thresholds above 7 g/dL to 8 g/dL [191,192]. It is generally prudent to consider the clinical context, the patient's willingness to accept blood products (e.g. Jehovah's Witness) and alternative therapies before making the decision to recommend blood transfusion.

In a recent meta-analysis, lower FFP: RBC ratio was associated with poorer 24-h and 30-day survival. High FFP: RBC ratio conferred survival benefits with the highest survival benefit at 1:1.5 [193].

Tranexamic acid (TXA) is an anti-fibrinolytic agent that binds to lysine receptors on plasmin to fibrin and inhibiting fibrinolysis. A Cochrane Review looking at the effectiveness of TXA in reducing blood loss during cytoreductive surgery for advanced ovarian cancer demonstrated no difference in the number of transfused units between the TXA group vs the placebo/no treatment group [194].

Prothrombin Complex Concentrate (PCC) is primarily indicated for the rapid reversal of the anticoagulant effects of vitamin K antagonists with certain advantages over FFP. The use of PCC has been advocated certain types of abdominal surgery (liver transplant), but there is little data for its use in CRS±HIPEC [195].

Restrictive blood transfusion policy

Summary and recommendation: Restrictive intraoperative transfusion policy with a haemoglobin threshold level of 8 g/dL an as option to less stringent values should be performed routinely considering morbidity, mortality, and survival concerns.

Evidence level: Moderate by indirectness.

Recommendation strength: Strong positive (91.7% agreement, consensus reached)

Preemptive use of fresh frozen plasma (FFP)

Summary and recommendation: NO consensus was reached on the preemptive/prophylactic treatment of coagulopathy during CRS±HIPEC with fresh frozen plasma, as an option to the traditional reactive policy, in order to reduce the red blood cell transfusion requirements.

Evidence level: Low by indirectness.

Recommendation strength: No consensus.

Tranexamic acid (TXA)

Summary and recommendation: Tranexamic acid alone or associated with cryoprecipitate could be administered to reduce the risk of bleeding during CRS±HIPEC.

Evidence level: Moderate by indirectness.

Recommendation strength: Weak negative (79.2% agreement, consensus reached)

Prothrombin complex concentrate (PCC)

Summary and recommendation: Prothrombin complex concentrate, as an option to FFP, could be administered (66.67% weak negative) for the rapid reversal of the anticoagulant effects of vitamin K antagonists.

Evidence level: Moderate by indirectness.

Recommendation strength: Weak negative (66.7% agreement, consensus reached)

Abdominal and thoracic drains

Recently published systematic reviews and meta-analyses have demonstrated that short-term surgical outcomes in terms of fistula, wound infections, pulmonary complications, length of in-hospital stay and postoperative mortality are not favored by routine abdominal drains after gastric cancer surgery [196], colorectal surgery [197–200] pancreatic resection [201,202] and liver surgery [203,204]. There is no study addressing the actual role of abdominal drains in CRS±HIPEC. Data against prophylactic use of drains in conventional abdominal surgery are very consistent, but it is unclear if they can be extrapolated to CRS±HIPEC that represents a particular surgical setting.

The occurrence of diaphragmatic procedures such as peritonectomy or full thickness muscle resection is quite frequent during CRS and there is no consensus regarding the prophylactic use of thoracostomy tubes to avoid postoperative pleural effusion or pneumothorax [205]. On the one hand, when thoracostomy tubes are not placed intraoperatively, a symptomatic pleural effusion may require thoracentesis or even postoperative placement of a chest drain. On the other hand, a prophylactic thoracostomy tube may result in malpositioning in up to 20% of cases, and in a minor proportion of cases, may lead to other complications like infection [206].

Available data on prophylactic use of intraoperative thoracostomy in patients submitted to diaphragmatic manoeuvres during cytoreduction are of low level of evidence. One single retrospective comparative study favors its use claiming the reduction of subsequent severe or symptomatic pleural effusion that could require thoracentesis and/or postoperative chest tubes. The routine thoracostomy placement is not complication-free and may lead to problems of malfunctioning, requiring repositioning.

Abdominal drains

Summary and recommendation: Prophylactic abdominal drains after CRS±HIPEC could be indicated to lower the risk of gastrointestinal fistula, wound infection, pulmonary complications, length of stay and mortality.

Evidence level: Low for CRS±HIPEC, high for other major abdominal surgeries.

Recommendation strength: Weak positive (50.0% agreement, consensus reached)

Thoracic drains

Summary and recommendation: Prophylactic thoracostomy after CRS±HIPEC with diaphragmatic peritonectomy ± full thickness muscle resection could be indicated to lower the risk of severe subsequent pleural effusion or pneumothorax.

Evidence level: Low.

Recommendation strength: Weak positive (54.2% agreement, consensus reached)

Early extubation

The rate of extubation of patients undergoing CRS±HIPEC in the operating room differs in every institution and in different patient populations vary from 62 to 100% [186,207,208]. Criteria for extubation in HIPEC patients have not been categorically defined and seem to vary with institutional practices and comfort of anaesthesiologist. A retrospective study observing reasons for increased morbidity and mortality in this patient population, associated ventilation more than 24 h with longer operative times, higher PCI, greater blood loss and higher needs for crystalloids, colloids and blood products with lower PaO_2/FIO_2 ratio [208]. High lactate levels during HIPEC was associated with prolonged ventilation [208]. Presence of metabolic acidosis is not considered a contraindication for extubation, as some degree of metabolic acidosis is observed in most of these patients [186]. Direct contact with authors suggested practice of early extubation on the OR table in nearly all patients in their practice after HIPEC surgery [76]. Early extubation allows for early ambulation and reduced number of days on sedation, leading to earlier return of bowel function and early recovery. Presence of an epidural catheter and local anaesthetic infusion are likely to reduce opioid requirements in the intraoperative and immediate postoperative phase. This facilitates early extubation.

Summary and recommendation: Early extubation should be done routinely after CRS±HIPEC in the absence of contra-indications, to reduce pulmonary complications, length of stay in ICU and hospital LOS.

Evidence level: Low by indirectness.

Recommendation strength: Strong positive (100.0% agreement, consensus reached)

Discussion

The ERAS guidelines for CRS±HIPEC represent a comprehensive set of recommendations regarding the performance of this complex and high-risk procedure. Unfortunately, the perioperative care of the combined procedure still lacks standardisation and is characterized by a wide variation in protocols across centres. The present evidence-based recommendations are timely and will enable a critical step forward in the evolution of perioperative management of patients affected by peritoneal surface malignancies.

According to recent recommendations [7,209], we adopted the GRADE methodology, which is a structured process for summarising evidence and for taking the steps required in developing recommendations. Following GRADE, we used the PICO approach to carefully frame questions, choose outcomes of interest, rate their importance and evaluate the evidence. The GRADE approach has the advantage of being transparent and including not only the evidence but also values and preferences of patients to arrive at recommendations.

One of the main limitations of the present recommendations is the paucity of direct evidence and the lower quality of evidence from extrapolated studies. Direct evidence from studies conducted specifically in CRS±HIPEC was available in only 8/72 items. Therefore, evidence was extracted from studies carried out in the setting of other related procedures like colorectal or major abdominal surgeries. During the pre-voting phase, the panellists and the core team deemed upon review of the literature, that the magnitude of the effects of 64/72 care items would not be the same in the context of CRS±HIPEC setting, due to specifics of pathophysiology. Therefore, the evidence was rated down by indirectness in 37 out of 64

remaining items, following the GRADE methodology [210]. In 17 out of 64 items the evidence was kept as in other surgical fields, despite indirectness. Most of these are interventions directly or indirectly related to modulation of metabolic and inflammatory response to surgical trauma, which are deemed to be the same in all types of surgeries. For instance, preoperative anaesthetic management, preoperative fasting and carbohydrate load, perioperative pain management, perioperative glucose control, and pre/postoperative nutritional management are all items related the control of the stress, development of insulin resistance, hyperglycemia, metabolism, and postsurgical inflammation.

Following the Delphi technique to achieve consensus, we conducted a well-structured two-round voting process that involved participants from diverse geographic locations with different areas of expertise that encompassed several disciplines. One of the main advantages of the Delphi technique is that we managed to avoid the situation where a specific expert might dominate the consensus process, ensuring quasi-anonymity in the process [211].

One of shortcomings of the Delphi technique is the fact that criteria for "consensus" are not clearly defined in the literature [211]. Given the paucity and low quality of underlying evidence and anticipating a high number of controversial issues, the authors chose modest thresholds ($\geq$50%). This cutoff was surpassed by far for most items. In fact, the panelists reached the consensus in 71 items, after the second round, with a mean rate of agreement of 78%. Moreover, consensus was so strong that it would have been reached in 74% of items, even if a far higher threshold of $\geq$75% were applied.

High degree of consensus and strong recommendations were issued notably for extensive preoperative work-up and optimisation. The latter includes, among other items, very complex, work-intensive and costly interventions such as smoking and alcohol cessation programmes, screening for sleep apnea, frailty screening, and prehabilitation. It remains to be seen how successful the implementation and compliance to these ambitious interventions will be in the majority of centres, including centres of excellence.

The recommendations for bowel preparation are controversial given the conflicting evidence that was generated recently. It is therefore consistent that only weak recommendations were found for the three related items: *weak positive* for bowel preparation for probable rectal resection, *weak positive* for oral antibiotic decontamination (even in the absence of mechanical bowel preparation) and *weak negative* against routine bowel preparation for probable colectomy in the context of CRS±HIPEC [212]

One interesting finding worth discussing was the considerable number of *strong positive* recommendations that were supported by low level evidence (n = 12) (Table 1) The panellists issued strong recommendations, particularly in low risk interventions, as they perceived a clear balance in favour of benefit against undesirable effects, despite the absence of unbiased randomised controlled studies. This happened in the care items 1, 2A, 2B, 4, 17, 20, 22, 23, 24, 25, 26 and 27. The interpretation, according to GRADE, is that these recommendations may change when higher quality evidence becomes available, and therefore, they represent topics that deserve priority for further research.

In summary, the best available evidence and a standardised expert consensus process were used to prepare ERAS recommendations for CRS±HIPEC. Clinicians are encouraged to use this guideline to optimise perioperative care for patients undergoing the high-risk combined procedure. Nonetheless, evidence in this field of surgery is lacking or weak and mostly based on indirectness. Therefore, it is prudent to implement these recommendations cautiously, while prospectively monitoring feasibility and results in routine clinical practice. Lastly, there is an urgent need to further investigate the different aspects of perioperative care for CRS±HIPEC to generate more and better primary evidence.

Disclosures

GN is Secretary of the ERAS® Society (no financial conflicts)

Contribution Author(s)

Study concepts: MH, JV, GN
Study design: MH, SK, LV, JV, GN
Data acquisition: ALL AUTHORS
Quality control of data and algorithms: MH, SK, LV, JV, GN, AA, WF
Data analysis and interpretation: MH, SK, LV, JV, GN
Statistical analysis: MH, SK, LV
Manuscript preparation: MH, SK, LV, JV, GN
Manuscript editing: ALL AUTHORS
Manuscript review: ALL AUTHORS

Declaration of competing interest

All other authors declare to have no disclosures.This information has been provided by all authors individually in their attached author forms with date and signatures.

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