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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 II: Postoperative management and special considerations

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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

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 II of the guidelines highlights postoperative management and special considerations.

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 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 strength of recommendations. A two-part series of guidelines was created based on the consensus of an expert panel. The previous Part I of the guidelines highlights preoperative and intraoperative management. The current 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 panel to evaluate using the Delphi technique. The two experts

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Table 1
List of ERAS Care Items: Postoperative items and special considerations.

III Postoperative phase and special considerations	
18. Nasogastric drainage	23. Postoperative control of glucose
19. Urinary indwelling catheter	24. Prophylaxis against thromboembolism
A *Early removal of urinary catheter*	A Mechanical thromboprophylaxis
B Removal of urinary catheter before epidurals	B Pharmacological thromboprophylaxis
20. Prevention of postoperative ileus (including use of postoperative laxatives)	C Extended pharmacological thromboprophylaxis
A Postoperative thoracic epidural analgesia	25. Prevention, early detection and treatment of HIPEC complications
B Postoperative use of selective μ-opioid receptor antagonists	A Early stop of anti-angiogenic medications
C Postoperative use of laxatives, prokinetics	B Prophylactic ureteral stenting
21. Postoperative analgesia	C High-dose of Cisplatin
A Postoperative thoracic epidural analgesia	D Use of sodium thiosulfate
B Combination analgesia with Paracetamol, NSAIDs and opioids	E Use of intraoperative loop diuretics and dopamine
C Postoperative use of alternative analgesia	F High-dose of Mitomycin C (MMC)
22. Perioperative nutritional care	G Post-operative administration of GCSF
A Early oral intake	26. Early Mobilisation
B Oral nutritional supplements	27. Post-discharge care after CRS/HIPEC
C Screening for insufficient intake	28. ERAS Audit and Reporting
D Preemptive enteral nutrition	
E Preemptive parenteral nutrition	

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 expert 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. 1.

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 *postoperative care items and special considerations* along with grade of evidence and strength of consensus (% of expert votes) (Table 3). Please note that sequence and numbering schema of the care items continues from those 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 I: Preoperative and Intraoperative Management.

Intraoperative phase (and special considerations)

Nasogastric drainage

The utility of routine decompression of the stomach with a nasogastric tube (NGT) after abdominal surgery has long been debated. Patients undergoing CRS ± HIPEC may experience slow return to bowel function due to extensive intraoperative bowel manipulation, lysis of adhesions, intraoperative fluid resuscitation and additive effects of hyperthermia and chemotherapy on ileus.

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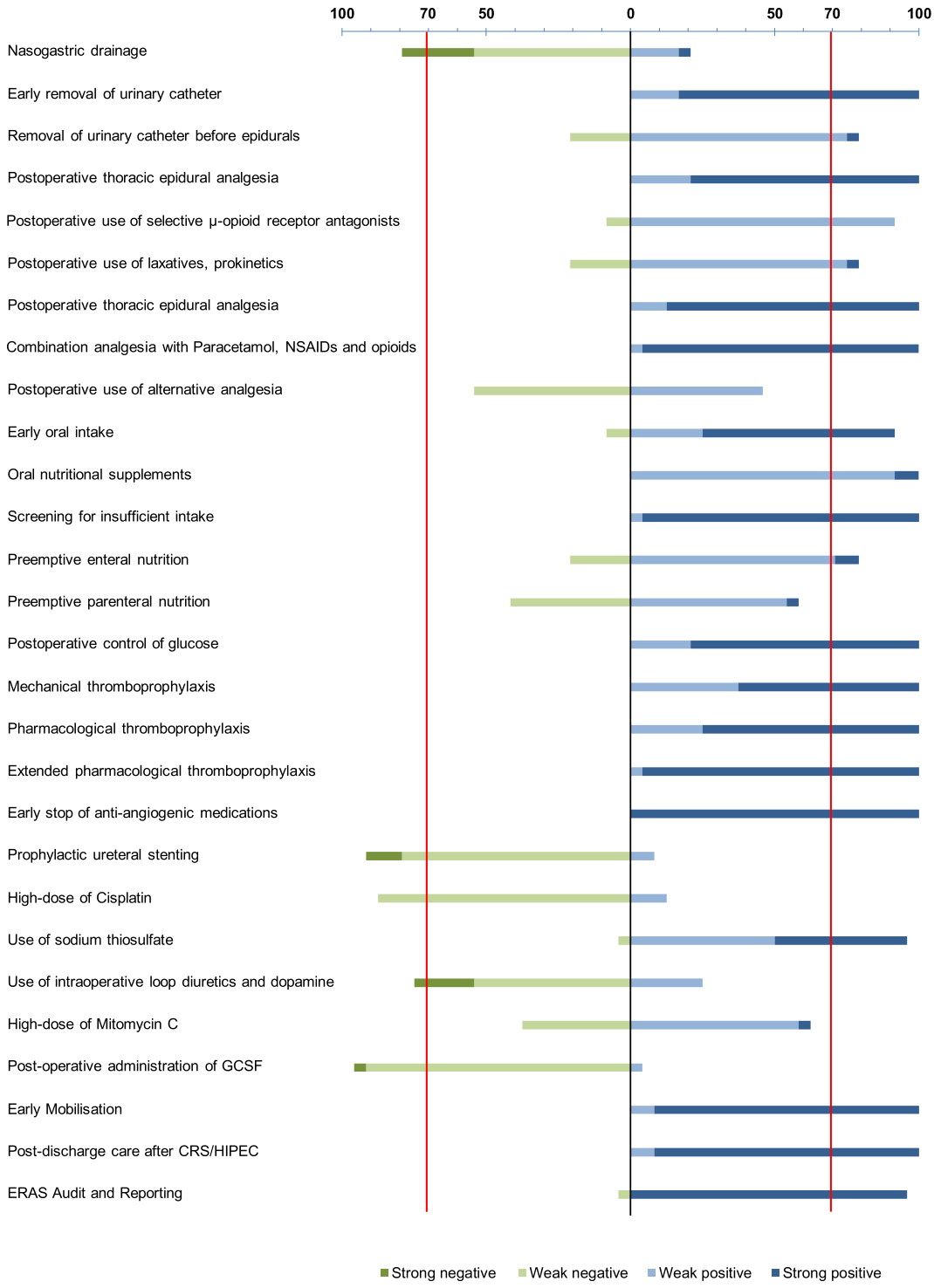

Fig. 1. Experts' voting for perioperative care items and clinical questions: postoperative items and special considerations.

However, the preponderance of data does not support the routine use of NGT in gastrointestinal surgery.

A meta-analysis of 26 trials, which included 3964 patients undergoing selective versus routine nasogastric decompression demonstrated decreased incidence of fever, atelectasis, and pneumonia as well as decreased number of days to first oral intake in patients not managed with NGT. While patients may have developed abdominal distension or vomiting without a tube, there is no associated increase in complication or hospital length of stay [10]. A Cochrane Review which included 33 studies, incorporating 5240 patients randomised to selective or no tube use versus routine tube use after abdominal surgery, revealed delayed return of bowel function and increased pulmonary complications in patients managed with routine tube use. Vomiting was decreased with routine tube use, but at the cost of increased discomfort. Length of stay was shorter when no tube was utilized [11]. A meta-analysis of 17 randomised controlled trials showed that NGT decompression did not provide any clinical benefits such as earlier recovery of

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

	Level of evidence				
Strength of recommendation	High	Moderate	Low	Very low	Total
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**

gastrointestinal function or reduction of postoperative complications. In fact, undesired effects such as discomfort and delayed resumption of a liquid or regular diet were demonstrated with no decrease in hospital length of stay [12]. A more recent meta-analysis of 7 studies with 1416 patients found that routine NGT use did not decrease the time to gastrointestinal function, but instead increased pharyngolaryngitis and respiratory infection [13].

Summary and recommendation: Prophylactic nasogastric drainage for CRS ± HIPEC, in the absence of risk factors for delayed gastric emptying (resection of lesser omentum) should not be done, as nasogastric decompression has been associated with undesired effects of delayed resumption of gastrointestinal motility and

Table 3
Postoperative ERAS recommendations and special considerations for cytoreductive surgery (CRS) with or without hyperthermic IntraPEritoneal chemotherapy (HIPEC).

Item	Recommendation	Evidence Level	Recommendation Strength
Postoperative phase			
Nasogastric drainage	Prophylactic nasogastric drainage should not be done	Moderate by indirectness	Weak negative
Urinary indwelling catheter	Removal of urinary catheter as early as postoperative day 3 is recommended	Moderate by indirectness	Strong positive
	Removal of urinary catheter before removal of the epidural catheter could be indicated	Moderate by indirectness	Weak positive
Prevention of postoperative	Thoracic epidural analgesia containing local anaesthetics and short-acting opiates is recommended to prevent ileus	Low for CRS ± HIPEC	Strong positive
	Use of selective μ-opioid receptor antagonist alvimopan (if available) could be indicated	Low for CRS ± HIPEC	Weak positive
	Laxatives, prokinetics and adjunct measures (coffee, chewing gum), alone/in combination, could be indicated	Low	Weak positive
Postoperative analgesia	Thoracic epidural analgesia containing local anaesthetics and short-acting opiates is recommended	High despite indirectness	Strong positive
	After TEA removal, analgesia with paracetamol (acetaminophen), NSAIDs and opioids is recommended	High despite indirectness	Strong positive
	After CRS ± HIPEC, alternative analgesia with ketamine, lidocaine or gabapentin is typically not indicated	Low	Weak negative
Perioperative nutritional care	Early oral intake aiming for clear liquids on the day of surgery and solid food from POD1 is recommended	Moderate by indirectness	Strong positive
	Oral nutritional supplements in addition to normal food after CRS ± HIPEC could be indicated	Low	Weak positive
	Recording of nutritional intake after CRS ± HIPEC to identify patients with insufficient intake is recommended routinely	Low	Strong positive
	Preemptive enteral nutrition after CRS ± HIPEC can be considered in selected patients	Low for CRS ± HIPEC	Weak negative
	Preemptive parenteral nutrition after CRS ± HIPEC (in addition to oral and/or enteral nutrition), is recommended in selected patients	Low for CRS ± HIPEC	Weak positive
Postoperative control of glucose	Monitoring of blood glucose in critically ill patients after CRS ± HIPEC and correction of glycaemia using short-acting insulin is recommended routinely	Low for CRS ± HIPEC	Strong positive
Prophylaxis against thromboembolism	Mechanical thromboprophylaxis until complete mobilisation in association with pharmacological thromboprophylaxis as an option to pharmacological thromboprophylaxis alone should be performed routinely	Low	Strong positive
	Pharmacological thromboprophylaxis started 12 h prior to CRS ± HIPEC should be performed routinely	Moderate by indirectness	Strong positive
	Extended pharmacological thromboprophylaxis until 4 weeks after CRS ± HIPEC, as an option in addition to in-hospital thromboprophylaxis should be performed routinely	Moderate for CRS ± HIPEC	Strong positive
Early Mobilisation	Mobilisation and physiotherapy starting the day of surgery (out of bed) with goals for > 2 h of physical exercises for POD 2 and > 6 h thereafter should be performed routinely	Low	Strong positive
Post-discharge care	Specific recommendations for nutritional care and physiotherapy after discharge in CRS ± HIPEC patient are recommended routinely	Low	Strong positive
ERAS Audit and Reporting	Audit of compliance with the ERAS pathway and of clinical outcomes to monitor the performance of the ERAS programme should be performed routinely	Moderate by indirectness	Strong positive
Special considerations			
Prevention, early detection and treatment of HIPEC complications	Discontinuation of bevacizumab or other anti-angiogenic treatment should be done routinely at least 5 weeks before CRS ± HIPEC	Low	Strong positive
	Prophylactic positioning of ureteral stents in patients with a high probability of pelvic peritonectomy should not be done routinely	Low	Weak negative
	Cisplatin dose >240 mg for HIPEC, considering concerns for nephrotoxicity and severe morbidity should not be given	Low	Weak negative
	Parenteral sodium thiosulfate before HIPEC with cisplatin could be performed	Low	Weak positive
	Intraoperative loop diuretics and dopamine for renal protection should not be performed routinely	Moderate	Weak negative
	Mitomycin C dose > 40 mg for HIPEC should be given only in patients without risk factors	Very low	Weak positive
	Postop administration of GCSF to prevent neutropenia should not be performed until white cell count is less than 500/mm3	Very low	Weak negative

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increased postoperative complications.

Evidence level: moderate by indirectness. Recommendation strength: Weak negative (54.2% agreement, consensus reached).

Urinary indwelling catheter

During and immediately after HIPEC surgery, it is important to maintain adequate organ perfusion and avoid intravascular volume depletion. Adding nephrotoxic chemotherapy in HIPEC, especially cisplatin, combined with hypoperfusion will increase the odds of having an acute kidney injury. Accordingly, bladder drainage is commonly utilized to monitor and maintain adequate urine output after surgery. The most critical time of renal perfusion is generally felt to be the first 24–48 h [14]. Prolonged use of urinary indwelling catheters (UIC), however, comes with adverse outcomes. Prolonged catheterization has been associated with two major poor clinical outcomes: catheter-associated urinary tract infection and postoperative delirium. Occurrence of catheter associated urinary tract infection is between 5.5 and 12.5/1000 catheter days [15], and it has been seen in up to 3–5% of hospitalized patients with UIC [16]. Delirium has also been seen in up to 30% in patients with urinary indwelling catheters who are in the intensive care unit [17]. The two aforementioned complications increase after 48 h from insertion.

A large observational study confirms low urinary retention rates (14%) in colorectal surgery and highlighted male gender and postoperative epidural analgesia as important independent predictors of retention [18].

Early removal of urinary catheter

Summary and recommendation: Removal of urinary catheter as early as the morning of postoperative day 3 *is recommended*.

Evidence level: moderate by indirectness. Recommendation strength: Strong positive (83.3% agreement, consensus reached).

Removal of urinary catheter before epidurals

Summary and recommendation: Removal of urinary catheter before removal of the epidural catheter could be indicated.

Evidence level: moderate by indirectness. Recommendation strength: Weak positive (75.0% agreement, consensus reached).

Prevention of postoperative ileus (including use of postoperative laxatives)

Cytoreductive surgery ± HIPEC requires adequate exploration of the whole abdomen and extensive manipulation of the small bowel, sometimes with several visceral resections, including frequently colorectal resection and anastomoses. One meta-analysis showed an incidence of prolonged postoperative ileus of 10.2% following elective colonic surgery [19], with potential higher rates with added effects of the hyperthermic bath, chemotherapy and peritoneal carcinomatosis [20,21].

Epidurals have been shown to improve postoperative pain control and decrease the rates of ileus in CRS [22]. Although earlier studies had not shown an obvious benefit to epidural local anaesthetics, a large Cochrane review in 2016, examined 128 trials with 8754 patients and showed decreased time to first bowel movement and decreased postoperative pain levels [23]. Mid-thoracic epidurals however can interfere with Foley removal and mobilisation, and therefore TAP block use has increased. Two small studies in CRS have shown that TAP blocks have lower rates of urinary retention and shorter hospital stay, but high pain scores then epidurals [24,25]. Intravenous lidocaine appears not to have any benefit to GI recovery, nausea or pain control [26]. Other ERAS interventions such as avoidance of nasogastric tubes, early oral feeding and mobilisation seem to reduce postoperative ileus [27,28].

Coffee consumption for the purpose of GI recovery remains controversial. Positive results have been found to decreasing ileus from 30% to 10% in gynaecology [29] and decrease time to first bowel movement in CRS [30], yet decaffeinated coffee showed shorter time to first bowel movement in a second CRS study [31]. Chewing gum is a safe and inexpensive intervention with a Cochrane review in 2015 examining 81 trials, showing a decreased time to bowel movement and flatus [32]. A subsequent trial in CRS in 2018 however, failed to show a benefit [33]. Several adjunct agents have been examined as well. Alvimopan and methylnaltrexone are peripheral μ-opioid receptor antagonist. Alvimopan was tested in nine RCTs (using 6–12 mg/oral dose) with overall net positive results [34]. Availability of alvimopan remains limited in Europe and Canada. Examination of methylnaltrexone in 2 RCTs showed no difference in time to discharge, nausea or vomiting [35]. Multiple pro-kinetic agents have failed to show benefit for ileus, including: diatrizoate meglumine (Gastrografin®) [36]; Ulimorelin [37], erythromycin, neostigmine, metoclopramide and cisapride [38]. Mosapride however has shown a decreased time to flatus and feces and increase in postop food intake [39]. Perioperative bisacodyl seems to be beneficial in a small RCT after colorectal surgery [40].

Postoperative thoracic epidural analgesia

Summary and recommendation: Thoracic epidural analgesia (TEA: T5-11) containing local anaesthetics and short-acting opiates for 72 h after CRS ± HIPEC is recommended to prevent postoperative ileus.

Evidence level: low for CRS ± HIPEC, high for comparable surgeries. Recommendation strength: Strong positive (79.2% agreement, consensus reached).

Postoperative use of selective μ-opioid receptor antagonists

Summary and recommendation: Low for CRS ± HIPEC, high for comparable surgeries.

After CRS ± HIPEC, the selective μ-opioid receptor antagonist almivopan (if available) could be indicated to prevent postoperative ileus.

Evidence level: low for CRS ± HIPEC, high for comparable surgeries. Recommendation strength: Weak positive (91.7% agreement, consensus reached).

Postoperative use of laxatives and prokinetics

Summary and recommendation: Laxatives, prokinetics and adjunct measures (coffee, chewing gum, etc), alone or in combination, could be indicated after CRS ± HIPEC to prevent postoperative ileus.

Evidence level: low. Recommendation strength: Weak positive (75.0% agreement, consensus reached).

Postoperative analgesia

The optimal analgesic regimen for major surgery should provide good pain relief, allow for early mobilisation, facilitate return of gut function and feeding and not cause complications [41]. There has been increasing recognition that analgesia should be process specific. The cornerstone of analgesia remains multimodal analgesia combining regional analgesia or local anaesthetic techniques and minimizing parenteral opioids with their side effects.

Cytoreductive surgery with or without HIPEC is almost always done via midline laparotomy. There is no prospective or

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randomised trial providing evidence for any superior analgesic regimen in CRS ± HIPEC. Recommendations are made from retrospective case series analysis, expert opinion and evidence from other major intra-abdominal surgeries.

Thoracic epidural analgesia (TEA) is regarded as the optimal technique following laparotomy [14,42], aiding in recovery of gut function, resulting in stability of anastomoses [43], reducing pulmonary complications [44] and yielding acceptable complication rates [45,46]. Epidural block should include segments T5-T11 47 and the infusion should start early during surgery [46]. A single centre retrospective analysis reported an improved survival after HIPEC when TEA was used compared to patient-controlled opioid analgesia opioids [48]. Similar results were found in CRS for epithelial ovarian cancer if TEA was used for more than 48 h postoperatively [49].

Using low-dose concentrations of local anaesthetic combined with a short-acting opiate appears to offer the best combination of analgesia while minimizing the risk of motor block and hypotension due to sympathetic blockade [50]. There is growing popularity for patient-controlled epidural analgesia compared to conventional continuous epidural infusion [51].

If epidurals are employed, the aim should be to remove the epidural 48–72 h postoperatively. There must be adherence to local policies, such as management of breakthrough pain, hypotension (using both fluids and vasoactive support) and neurological monitoring to detect the early onset vertebral canal space occupying lesions from haematomata and abscesses [46].

Paracetamol/acetaminophen is a vital part of multimodal analgesia. It is available both as an oral and an intravenous preparation and is usually administered as 1 gm four times daily. NSAIDs can be given orally or intravenously but should be considered carefully if there is a risk of renal dysfunction [50]. In some countries dipyrone/metamizol is used as an alternative, but in many parts of the world, it is not available because of the risk of agranulocytosis. There are some reports of several other drugs used for analgesia to avoid the use of opioids like lidocaine, ketamine or gabapentin. Currently, none of them can be recommended for routine use at this time as further studies are required.

Postoperative thoracic epidural analgesia

Summary and recommendation: Thoracic epidural analgesia (TEA: T5-11) containing local anaesthetics and short-acting opiates for at least 72 h after CRS ± HIPEC is recommended as an option to intravenous opiates for postoperative analgesia.

Evidence level: high despite indirectness. Recommendation strength: Strong positive (87.5% agreement, consensus reached).

Combination analgesia with paracetamol (acetaminophen), NSAIDs and opioids

Summary and recommendation: After TEA removal, analgesia with paracetamol (acetaminophen), NSAIDs and opioids is recommended.

Evidence level: high despite indirectness. Recommendation strength: Strong positive (95.8% agreement, consensus reached).

Postoperative use of alternative analgesia

Summary and recommendation: After CRS ± HIPEC, alternative analgesia with ketamine, lidocaine or gabapentin is typically not indicated.

Evidence level: low. Recommendation strength: Weak negative (54.2% agreement, consensus reached).

Perioperative nutritional care

It is a commonly held belief that gastrointestinal recovery after CRS ± HIPEC takes longer when compared to other surgical procedures [52]. Preoperative nutritional status may predict length of stay, risk of infectious complications and possibly longer term survival. Assessing the nutritional state of a patient is a critical step preoperatively as noted in a different section [53–55]. Further, there is significant variability in postoperative nutritional support for this patient group [54]. Readmissions occur in 11–25% of patients and in one study, ileus/dehydration was responsible for one third of readmissions [56,57]. Despite this, a review of best practice in CRS ± HIPEC recommends an early start of enteral nutrition including patients with peritonectomy procedures and HIPEC [58].

One prospective series reported on 156 consecutive patients who underwent a fast track protocol after CRS and HIPEC [27]. Components of the protocol related to perioperative nutrition included a low residue diet one week preoperatively, sugary drinks one day preoperatively, early oral feeding introduced in the first postoperative day, liquids only for postoperative days 1–2, soft diet postoperative days 3–5 and full diet thereafter. Ileus occurred in 10 patients (5.8%) and nasogastric tube was introduced in 6 (3.8%). Oral nutritional supplements were not specifically mentioned in this series. Length of stay as well as perioperative complications appeared lower than most of the literature but there was no comparison group.

Extrapolation from ERAS guidelines in colorectal surgery may be considered. A Cochrane review notes early postoperative nutritional support is associated with shorter length of stay, fewer complications and decreased mortality. However, the review suggests caution in interpretation due to heterogeneity of studies and lower quality of evidence [59]. A meta-analysis notes early oral nutrition was a component of all enhanced recovery programmes in colorectal surgery [60]. A randomised trial supports a low residue diet over clear fluids in the prevention of postoperative ileus leading to less nausea, faster return of bowel function and shorter length of stay [61]. Oral nutritional supplements are not supported by randomised trials but a prospective series suggests a role for protein rich supplements as part of an ERAS programme [62].

In patients where gastrointestinal complications or ileus prevents oral intake, one should consider parenteral nutrition (PN). A review of best practice recommends early supplemental PN be considered if delays greater than 3 days are anticipated [58] (5 days according to ESPEN guidelines). All patients started PN postoperative day 1 in a retrospective series of 321 patients undergoing CRS and HIPEC [63]. Of note, median duration of PN was 9 days (range 1-87d); 19 patients (6%) required PN for less than 5 days and 42 patients (13%) required PN for less than 7 days. A survey indicated that nutritional support was routinely supplemented postoperatively by 59% of high-volume surgeons, most commonly with PN [64]. Another series found feeding tube placement during CRS and HIPEC did not improve postoperative nutritional status and was associated with longer length of stay [65].

Early oral intake

Summary and recommendation: Early oral intake resumption after CRS ± HIPEC, aiming for clear liquids on the day of surgery and solid food from postoperative day 1, in the absence of risk factors for delayed gastric emptying (resection of lesser omentum), is recommended to improve mortality, anastomotic dehiscence, resumption of bowel function and hospital length of stay.

Evidence level: moderate by indirectness. Recommendation strength: Strong positive (66.7% agreement, consensus reached).

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Oral nutritional supplements

Summary and recommendation: Oral nutritional supplements (protein-rich, 2–3/day) in addition to normal food after CRS ± HIPEC could be indicated in order to help maximise sufficient energy and protein intake within the first 5 postoperative days.

Evidence level: low. Recommendation strength: Weak positive (91.7% agreement, consensus reached).

Screening for insufficient intake

Summary and recommendation: Daily recording of nutritional intake after CRS ± HIPEC in order to identify patients with insufficient intake is recommended routinely.

Evidence level: low. Recommendation strength: Strong positive (95.8% agreement, consensus reached).

Preemptive enteral nutrition

Summary and recommendation: Preemptive enteral nutrition (via feeding catheters) after CRS ± HIPEC for 7 postoperative days can be considered in selected patients (with expected insufficient oral intake) to reduce morbidity/mortality.

Evidence level: low for CRS/HIPEC, moderate for comparable surgeries. Recommendation strength: Weak negative (70.8% agreement, consensus reached).

Preemptive parenteral nutrition

Summary and recommendation: Preemptive parenteral nutrition after CRS ± HIPEC (in addition to oral and/or enteral nutrition), for 7 postoperative days is recommend in selected patients (expected insufficient oral/enteral intake).

Evidence level: low for CRS ± HIPEC, moderate for comparable surgeries. Recommendation strength: Weak positive (54.2% agreement, consensus reached).

Postoperative control of glucose

Surgical patients who have uncontrolled hyperglycaemia have a higher mortality rate and worse outcomes than patients who are normoglycaemic [66,67]. In addition, severe hypoglycaemia due to tight glucose control strategies is associated with increased mortality. However, the optimal blood glucose range is controversial [68]. Numerous clinical trials have compared different ranges of blood glucose in various populations of critically ill patients, but there is no data for CRS and HIPEC. Trials in surgical patients have reported mixed outcomes from intensive insulin therapy (IIT) [69,70]. In adult surgical patients, IIT (target blood glucose of 80–110 mg/dL [4.4–6.1 mmol/L]) increased the incidence of severe hypoglycaemia and either increased mortality or had no effect on mortality, when compared to more permissive blood glucose ranges of 140–180 mg/dL (7.8–10 mmol/L) and 180–200 mg/dL (19–11.1 mmol/L). There is no universally accepted insulin regimen of glycaemic control in critically ill patients. To avoid prolonged hypoglycaemia, insulin infusions and intermittent short-acting insulin can be used [71]. Blood glucose should be carefully monitored to achieve the target range and avoid hypoglycaemia.

Summary and recommendation: Monitoring of blood glucose in critically ill patients after CRS ± HIPEC and correction of glycaemia using short-acting insulin to keep blood glucose levels at 140–180 mg/dL (7.8–10 mmol/L) are recommended routinely in order to reduce postoperative mortality.

Evidence level: low for CRS ± HIPEC, high for critically-ill patients. Recommendation strength: Strong positive (79.2% agreement, consensus reached).

Prophylaxis against thromboembolism

Cytoreductive surgery with HIPEC is associated with a 30–50% venous thromboembolism (VTE) risk in the absence of prophylaxis [72,73], with grade [74–76] thromboembolic events range from 0 to 13.5% with pulmonary embolism of 4.4% [77]. Risk factors include disease burden, blood transfusion, and extent of surgery, Peritoneal cancer index, blood loss, operative time, lengths of hospital and intensive care unit stay, and lack of administration of anticoagulation at discharge [76]. VTE has been reported as the most common cause of death at 30 days after surgery in cancer patients [78]. Even though there are no established guidelines for thromboprophylaxis in patient undergoing HIPEC, standard guidelines for major cancer surgery [79,80] can be extrapolated to CRS ± HIPEC.

Early ambulation is advised whenever feasible, with patients out of bed by postoperative day 1. Mechanical prophylaxis by means of intermittent pneumatic compression (IPC) is advised until the patient is completely mobilised. Pharmacological thromboprophylaxis is advised unless there is contraindication for anticoagulation. Low molecular weight heparin (dalteparin or enoxaparin), fondaparinux and unfractionated heparin are the most common agents. The first dose is typically given 12 h before surgery and continued for a total 4 weeks as these patients are high risk.

Established guidelines support extended thromboprophylaxis (ETP) in high-risk patients after abdominal or pelvic surgery for cancer [80]. A retrospective study showed that 1/3 of VTE occurred during the inpatient admission, while 2/3 occurred in patients after discharge. Extended thromboprophylaxis reduced the 60-day VTE rate from 10.2 to 4.9%. Extended thromboprophylaxis after abdominal or pelvic surgery for cancer reduces the incidence of all VTEs and proximal DVTs, without any impact on symptomatic PE, major bleeding or 3-month mortality [81].

Mechanical thromboprophylaxis

Summary and recommendation: Mechanical thromboprophylaxis (intermittent pneumatic compression) until complete mobilisation in association with pharmacological thromboprophylaxis as an option to pharmacological thromboprophylaxis alone should be performed routinely.

Evidence level: low. Recommendation strength: Strong positive (62.5% agreement, consensus reached).

Pharmacological thromboprophylaxis

Summary and recommendation: Pharmacological thromboprophylaxis (low molecular weight heparin, unfractionated heparin or fondaparinux) started 12 h prior to CRS ± HIPEC should be performed routinely.

Evidence level: moderate by indirectness. Recommendation strength: Strong positive (75.0% agreement, consensus reached).

Extended pharmacological thromboprophylaxis

Summary and recommendation: Extended pharmacological thromboprophylaxis until 4 weeks after CRS ± HIPEC, as an option in addition to in-hospital thromboprophylaxis should be performed routinely to reduce the risk of asymptomatic deep vein thrombosis (not pulmonary embolism).

Evidence level: moderate for CRS/HIPEC. Recommendation strength: Strong positive (95.8% agreement, consensus reached).

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Prevention, early detection and treatment of HIPEC complications

There is significant potential morbidity following CRS and HIPEC with rates ranging between 18.7 and 52.5% [82]. The majority are related to surgical complications but this section will focus on complications related to the HIPEC portion of the procedure.

Systemic chemotherapy should be stopped at least 3 weeks before surgery. Agents that block vascular endothelial growth factor (VEGF) activity (bevacizumab, aflibercept) should be discontinued at least 5 weeks before surgery [83].

According to two retrospective non-comparative studies, prophylactic ureteral stenting may reduce rates of iatrogenic ureteral injuries but the procedure may also be associated with stent-related complications, such as bleeding and infection and increased LOS [84,85].

The risk of postoperative renal dysfunction is significant (1.3–5.7%) and multifactorial [86]. Cisplatin has a number of toxicities including ototoxicity, myelosuppression and allergic reactions but its main dose-limiting side effect is nephrotoxicity. Doses greater than 240 mg were correlated not only with increased severe morbidity but also with increased creatinine levels [87,88]. The risk of renal failure may be avoided by the systematic use of a renal protector, sodium thiosulfate. No renal failure occurred in a recent randomised controlled trial that evaluated the benefit of HIPEC with high dose of cisplatin (100 mg/m^2) in advanced ovarian cancer when sodium thiosulfate was used [8]. Mitomycin C can also less commonly lead to nephrotoxicity.

Optimising intravascular volume, cardiac output, and oxygen delivery by haemodynamic monitoring and goal-directed therapy fluid resuscitation in the operating room is likely the best method of preventing and/or treating nephrotoxicity [58]. Avoidance of additional nephrotoxic agents and agents that contribute to haemodynamic instability is logical [89]. Although used in some centres, low dose dopamine and loop diuretics have evidence against their use in critical care scenarios [89,90]. These practices are recommended by the European Society of Clinical Pharmacy Special Interest Group on Cancer Care for preventing cisplatin nephrotoxicity [91].

Myelosuppression appears to be primarily related to the type of agent used, most commonly Mitomycin C. Using a dose of 35 mg/m^2 over 90 min of HIPEC can result in postoperative neutropenia/leucopenia in as many as 27% of patients [86]. Using a fixed dose of 40 mg of Mitomycin C has been shown to results in a lower risk of leucopenia (7%) and neutropenia (4.5%) [92]. Routine prophylactic granulocyte colony-stimulating factor does not appear to alter neutropenia rates but may be used to avoid or prevent profound aplasia when white cell counts are decreasing [83,93].

An established clinical pathway incorporating patient selection, standardised nutrition, renal protection, pain management, prevention and early detection of complications reduced the failure to rescue from complications in one specialised institutional study [83].

Early discontinuation of anti-angiogenic medications

Summary and recommendation: Discontinuation of bevacizumab or other anti-angiogenic treatment should be done routinely at least 5 weeks before CRS ± HIPEC in order to reduce intraoperative bleeding complications.

Evidence level: low. Recommendation strength: Strong positive (100.0% agreement, consensus reached).

Prophylactic ureteral stenting

Summary and recommendation: Prophylactic positioning of ureteral stents in patients with a high probability of pelvic peritonectomy should not be done routinely to reduce the risk of ureteral complications.

Evidence level: low. Recommendation strength: Weak negative (79.2% agreement, consensus reached).

High-dose of cisplatin

Summary and recommendation: Cisplatin dose >240 mg for HIPEC, considering concerns on nephrotoxicity and severe morbidity should not be given.

Evidence level: low. Recommendation strength: Weak negative (87.5% agreement, consensus reached).

Use of sodium thiosulfate

Summary and recommendation: Parenteral sodium thiosulfate before HIPEC with cisplatin could be performed to avoid nephrotoxicity.

Evidence level: low. Recommendation strength: Weak positive (50.0% agreement, consensus reached).

Use of intraoperative loop diuretics and dopamine

Summary and recommendation: Intraoperative loop diuretics and dopamine for renal protection should not be performed routinely in patients undergoing CRS and HIPEC.

Evidence level: moderate. Recommendation strength: Weak negative (54.2% agreement, consensus reached).

High-dose of mitomycin C (MMC)

Summary and recommendation: Mitomycin C dose > 40 mg for HIPEC should be given only in patients without risk factors with special attention to potential myelosuppression.

Evidence level: very low. Recommendation strength: Weak positive (58.3% agreement, consensus reached).

Post-operative administration of granulocyte colony-stimulating factor (GCSF)

Summary and recommendation: Post-operative administration of GCSF to prevent neutropenia should not be performed until white cell count is less than 500/mm^3.

Evidence level: very low. Recommendation strength: Weak negative (91.7% agreement, consensus reached).

Early mobilisation

Although no studies are available in the literature on the effects of early mobilisation in patients after CRS ± HIPEC, benefits are likely to be similar as those seen in comparable surgeries [4]. Indeed, prolonged bed rest is associated with risk for developing pulmonary complications, decreased skeletal muscle strength, thromboembolic complications and insulin resistance [94].

Early mobilisation has therefore been an integral component of ERAS protocols. However, while there is strong evidence regarding the harmful effects of immobilisation, evidence is more limited regarding the benefit of dedicated interventions specifically designed to increase early mobilisation after surgery [95].

Risk factors for reduced early mobilisation in patients undergoing CRS and HIPEC are ICU stay, continued intravenous fluids, presence of intraperitoneal drainages, and prolonged indwelling urinary catheter [64]. All of these procedures are common in patients receiving HIPEC, but may be reduced and rehabilitation programme can be offered to this subset of patients [95].

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Summary and recommendation: Mobilisation and physiotherapy as early as the day of surgery (out of bed) with goals for > 2 h of physical exercises for postoperative day 2 and > 6 h thereafter should be performed routinely after CRS ± HIPEC to improve capacity to perform out-of-bed activities, facilitate resumption of gastrointestinal function and decrease postoperative complications.

Evidence level: low. Recommendation strength: Strong positive (91.7% agreement, consensus reached).

Post-discharge care after CRS/HIPEC

Cytoreductive surgery with or without HIPEC carries significant risk of morbidity, with 30-, and 90-day readmission rates as high as 15% and 21%, respectively [96]. The most common reasons for readmission include pain, abscess, malnutrition and bowel obstruction. While ERAS protocols in general have been shown to reduce readmission rates [1], it is less clear what specific recommendations (e.g. nutritional care, physiotherapy) should be made post discharge in patients undergoing major CRS ± HIPEC that may directly help decrease readmission. Further research in this area is required.

What is clearer, however, is that patients should be included in the discharge decision making process. This has been shown in studies emphasising that patients' informational needs should be met before discharge to help ensure successful self-management at home [97]; improved postoperative education and closer follow-up may lead to a substantial reduction in unnecessary hospital readmissions [98].

Summary and recommendation: Specific recommendations for nutritional care and physiotherapy after discharge in CRS ± HIPEC patient are recommended routinely.

Evidence level: low. Recommendation strength: Strong positive (91.7% agreement, consensus reached).

ERAS audit and reporting

The importance of audit and reporting of both clinical outcomes and compliance within ERAS programmes is well established [4,5]. It is not simply enough to follow an ERAS protocol but rather develop a multidisciplinary team that reviews ERAS protocol compliance and iterates towards improved outcomes [99,100]. Several multicentre studies in colorectal surgery have now shown that increasing ERAS element compliance is associated with a decrease in hospital length of stay [2], complications [101] and improved 5-year cancer-specific survival [102]. There is limited data in CRS patients. However, in a recent multicentre study of 2101 patients that included multi-visceral surgery for advanced ovarian cancer, the authors reported that improved compliance with ERAS gynaecologic oncology guidelines was associated with an improvement in clinical outcomes, including length of stay and complications [3]. A small single institution study of 31 patients undergoing CRS and HIPEC associated reductions in length of stay with implementation of an ERAS protocol [103]. A limitation of this study was that data on ERAS element compliance were not reported.

It is essential that the correct data elements and outcomes are collected as part of the ERAS audit as insufficient reporting of compliance may lead to incorrect conclusions [4]. To address the heterogeneity in ERAS reporting, ERAS USA and the ERAS Society have published the Reporting on ERAS Compliance, Outcomes and Elements Research (RECOvER) Checklist [104]. This checklist describes best practices for reporting clinical pathways and describing compliance. ERAS teams are encouraged to use auditing tools such as the ERAS Interactive Audit System (EIAS) [105] and REDCap system [106]. More recently, an international panel of experts has proposed an ERAS training curriculum, a framework for successful implementation, methods for assessing effectiveness of training and a definition of ERAS training centres of excellence [107].

Summary and recommendation: Audit of compliance with the pathway and of clinical outcomes to monitor the performance of the ERAS programme and to improve clinical practice should be performed routinely.

Evidence level: moderate by indirectness. Recommendation strength: Strong positive (95.8% 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 [7,108], 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 [109]. 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, perioperative 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 [110].

One of shortcomings of the Delphi technique is the fact that criteria for "consensus" are not clearly defined in the literature [110]. Given the paucity and low quality of underlying evidence and anticipating a high number of controversial issues, the authors chose modest thresholds (≥50%). This cutoff was surpassed by far

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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 ≥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.

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.

Strength of recommendation for the individual items is indicated by the colour code:

Strong positive:	dark blue	Weak positive:	light blue
Strong negative:	dark green	Weak negative:	light green

Consensus was reached for >50% of votes for one of the individual options above or for >70% of votes for either positive (weak or strong) or negative (weak or strong), respectively, as indicated by the red vertical lines.

CRediT authorship contribution statement

Martin Hübner: Conceptualization, Funding acquisition, Formal analysis, Writing - original draft, Writing - review & editing. **Shigeki Kusamura:** Funding acquisition, Formal analysis, Writing - original draft, Writing - review & editing. **Laurent Villeneuve:** Funding acquisition, Formal analysis, Writing - original draft, Writing - review & editing. **Ahmed Al-Niaimi:** Funding acquisition, Writing - original draft, Writing - review & editing. **Mohammad Alyami:** Funding acquisition, Writing - original draft, Writing - review & editing. **Konstantin Balonov:** Funding acquisition, Writing - original draft, Writing - review & editing. **John Bell:** Funding acquisition, Writing - original draft, Writing - review & editing. **Robert Bristow:** Funding acquisition, Writing - original draft, Writing - review & editing. **Delia Cortés Guiral:** Funding acquisition, Writing - original draft, Writing - review & editing. **Anna Fagotti:** Funding acquisition, Writing - original draft, Writing - review & editing. **Luiz Fernando R. Falcão:** Funding acquisition, Writing - original draft, Writing - review & editing. **Olivier Glehen:** Funding acquisition, Writing - original draft, Writing - review & editing. **Laura Lambert:** Funding acquisition, Writing - original draft, Writing - review & editing. **Lloyd Mack:** Funding acquisition, Writing - original draft, Writing - review & editing. **Tino Muenster:** Funding acquisition, Writing - original draft, Writing - review & editing. **Pompiliu Piso:** Funding acquisition, Writing - original draft, Writing - review & editing. **Marc Pocard:** Funding acquisition, Writing - original draft, Writing - review & editing. **Beate Rau:** Funding acquisition, Writing - original draft, Writing - review & editing. **Olivia Sgarbura:** Funding acquisition, Writing - original draft, Writing - review & editing. **S.P. Somashekhar:** Funding acquisition, Writing - original draft, Writing - review & editing. **Anupama Wadhwa:** Funding acquisition, Writing - original draft, Writing - review & editing. **Alon Altman:** Funding acquisition, Writing - original draft, Writing - review & editing. **William Fawcett:** Funding acquisition, Writing - original draft, Writing - review & editing. **Jula Veerapong:** Conceptualization, Funding acquisition, Formal analysis, Writing - original draft, Writing - review & editing. **Gregg Nelson:** Conceptualization, Funding acquisition, Formal analysis, Writing - original draft, Writing - review & editing.

Declaration of competing interest

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

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