Prehabilitation to improve postoperative outcomes in patients with peritoneal carcinomatosis undergoing hyperthermic intraperitoneal chemotherapy (HIPEC): A scoping review

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Abstract

Background: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) leads to increased survival rates in patients with peritoneal carcinomatosis, but is associated with considerable morbidity and mortality rates. Prehabilitation, a process to optimize a patient's preoperative functional capacity, has a positive impact on recovery after colorectal surgery. The impact of prehabilitation in patients undergoing HIPEC is scarcely investigated. This scoping review and narrative synthesis aims to summarize and evaluate what is currently reported about the effect of prehabilitation on postoperative outcomes after HIPEC.

Methods: A literature search of studies reporting on the effect of prehabilitation on outcomes after HIPEC was performed (August 2020). Study characteristics, patient demographics, composition of prehabilitation programs, and reported outcomes used to quantify the effect of prehabilitation were recorded.

Results: The literature search did not yield any studies on the effect of prehabilitation programs on outcomes after HIPEC. As an alternative, studies identifying modifiable risk factors for poor postoperative outcomes after HIPEC that can be targeted by prehabilitation were reviewed to evaluate starting points for prehabilitation. Fourteen studies identify the following preoperative factors: poor nutritional status, poor performance status, low health related quality of life and an history of smoking.

Conclusion: No research has been published on the effect of prehabilitation prior to HIPEC. This review demonstrates that preoperative modifiable risk factors for outcomes in patients undergoing HIPEC are multifactorial. A multimodal prehabilitation program prior to HIPEC, including nutritional support, psychical exercise, psychological support and smoking cessation, might therefore be a promising approach to improve postoperative outcomes.

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1. Introduction

Colorectal cancer is the second most common type of cancer worldwide [1]. Up to 40% of colorectal cancer patients develop peritoneal carcinomatosis which is associated with poor survival rates. The introduction of cytoreductive surgery in combination with hyperthermic intraperitoneal chemotherapy (HIPEC) as a standard of care for patients with peritoneal metastases has led to increased survival rates from 12.6 months, if treated with systemic chemotherapy and/or palliative surgery, to 22.3 months, if treated with HIPEC [2].

HIPEC is associated with 30-day major complications (Clavien-Dindo classification grade of 3 or higher) occurring in up to one-third of patients [3–5]. Such postoperative complications lead to higher mortality rates and impaired quality of life (QoL) [6,7]. Furthermore, even in the absence of complications, major procedures like HIPEC are associated with a reduction in functional capacity of 20–40% [8]; the surgical stress response activates a wide range of physiological effects, which seriously and directly impair cardiopulmonary and muscle function [9]. On top of this,
postoperative bed rest during hospitalization contributes to a progressive reduction of function capacity via a loss of muscle mass and function [10].

Developments, such as minimally invasive surgery and the ‘enhanced recovery after surgery’ (ERAS) protocol, targeted the perioperative and postoperative period to improve outcomes in patients undergoing surgery. Single center research however shows that the introduction of a prehabilitation program, focusing on the preoperative period, has led to a decrease of postoperative complications by 51% in other fields of surgery than HIPEC [11]. Moreover, 81% of patients undergoing a prehabilitation program is fully recovered in 8 weeks after colorectal surgery, while this is only 40% in patients not undergoing such a program [12].

These results might suggest that a prehabilitation program improves postoperative outcomes in patients with peritoneal carcinomatosis undergoing HIPEC, but the exact impact is unknown. In this scoping review, the primary research question was to evaluate and summarize the published studies that compared the effect of prehabilitation compared to standard preoperative work-up on postoperative outcomes after HIPEC.

2. Methods

2.1. Search strategy

A comprehensive search of published articles on the effect of unimodal or multimodal prehabilitation programs on postoperative outcomes in patients undergoing HIPEC was conducted. PubMed, Medline, Embase, Cochrane Library and Google Scholar databases were searched systematically. The complete search strategy included thesaurus terms (MeSH, Subject Headings and EMTREE) and keywords as shown in Appendix 1. Search results were supplemented by a hand search of the reference lists of all included studies.

2.2. Study selection

This review included randomized controlled trials, cohort studies and reviews that investigated the effect of unimodal or multimodal prehabilitation programs on postoperative outcomes after HIPEC. These programs could include any modality (physical exercise, nutritional support, psychological support and/or smoking cessation). Studies including patients undergoing other types of surgery were excluded. Animal studies, case reports and publications in other languages than English were excluded as well as unpublished studies without a full text available.

After screening for titles and abstracts, the articles meeting the inclusion criteria were identified and their full-text publications were reviewed by two researchers (DS and BvDH) independently. Disagreements regarding inclusion or exclusion of the selected studies were discussed to reach consensus.

2.3. Risk of bias assessment

The risk of bias of each included study was assessed using the Cochrane Risk of Bias (RoB) 2 tool [13] for randomized controlled, the Quality in Prognostic Studies (QUIPS) tool [14] for cohort studies, and the AMSTAR 2 checklist [15] for reviews. Any discrepancies were resolved by discussion.

2.4. Data extraction

Two reviewers (DS and BvDH) independently identified and extracted data from the studies included in this review. Study characteristics, patient demographics, composition of prehabilitation programs and reported outcomes (e.g., morbidity rates, mortality rates, survival rates) were used to quantify the effect of prehabilitation programs.

In case no articles were found, we hypothesized that risk factors for poor postoperative outcomes could be identified based on the literature search. Since prehabilitation is the optimization of these risk factors with the intent of improving postoperative outcomes, the subsequent step is to identify and evaluate which factors can be targeted preoperatively. This is valuable for future application of prehabilitation programs for patients undergoing HIPEC, not only for patients with colorectal cancer peritoneal metastases, but also for patients with pseudomyxoma peritonei, peritoneal mesothelioma, and peritoneal carcinomatosis for ovarian cancer, appendiceal cancer and gastric cancer.

3. Results

The final literature search was performed on August 18th, 2020 which resulted in 2,743 records after removal of duplications. The flow diagram is illustrated in Fig. 1. Title and abstracts screening identified 118 records eligible for full text screening. Of the 118 articles included in the full text review, 66 records were conference abstracts without a full text available. One study was identified with recommendations on multimodal prehabilitation to improve outcomes after HIPEC [16]. No randomized controlled trials, cohort studies or reviews investigating the effect of prehabilitation programs on postoperative outcomes in patients undergoing HIPEC were identified from the full text review.

Therefore, the literature search was used to identify and evaluate modifiable risk factors that can be targeted by prehabilitation. All 2,743 articles were re-screened to answer this alternative research question. A first step was to identify studies reporting on postoperative outcomes in patients undergoing HIPEC and then, to assess which studies provide information on factors influencing these outcomes. Fig. 2 illustrates the flow diagram of the selection of articles. Fifty studies provide important information outlining the postoperative outcomes in terms of postoperative morbidity, and mortality, length of hospital stay, and overall survival. These articles were systematically reviewed to explore which studies report on preoperative factors affecting postoperative outcomes. To evaluate possible starting points of a prehabilitation program in patients undergoing HIPEC, the results of 14 studies [17–30] identifying risk factors for poor postoperative outcomes that are modifiable and thus can be targeted preoperatively were summarized.

3.1. Preoperative modifiable factors influencing postoperative complications and mortality

Cohort studies performed between 2010 and 2015 show that major complication rates in patients undergoing HIPEC for colorectal cancer peritoneal metastases, stated as a Clavien-Dindo classification grade of 3 or higher, vary from 17 to 52% and mortality rates from 0 to 8%. A single center study in France [30], including 401 patients, shows an overall major complication rate of 13% and an overall mortality rate of 1% for patients undergoing HIPEC for peritoneal carcinomatosis, including pseudomyxoma peritonei, peritoneal mesothelioma, and peritoneal carcinomatosis from colorectal cancer, ovarian cancer, appendiceal cancer and gastric cancer.

Multiple studies identify modifiable factors that are significantly associated with higher postoperative complication rates and mortality. An overview of these studies and their reported results is shown in Table 1.

Patients with a poor nutritional status, defined as Subjective Global Assessment (SGA) score B or C, seem to be at higher risk of
Fig. 1. Flow diagram of primary research question.

Fig. 2. Flow diagram of alternative research question.
developing infectious complications postoperatively [17]. A cohort study by Van Vugt et al. [18] shows that a lower muscle index, associated with malnutrition, is a risk factor for postoperative morbidity. The presence of sarcopenia, muscle loss which can be a result of malnutrition, is found to be associated with higher likelihood of morbidity [19]. Both studies use cutoff values for muscle depletion, also defined as sarcopenia, of 52.4cm²/m² for men and 38.5cm²/m² for women, according to Prado et al. [31]. Reece et al. [20] do not find malnutrition, stated as SGA-B or −C, to be an independent predictor of complications after HIPEC, but they do find a significant association between malnutrition and infectious complications. These results suggest the importance of the preoperative nutritional status in patients undergoing HIPEC.

An impaired physical status of a patient seems to be a predictive factor for poor postoperative outcomes; three studies show that a preoperative Eastern Cooperative Oncology Group (ECOG) performance status higher than 0 (fully active), which describes an increased level of functioning in patients, gives an 2- to 6-fold increased risk on postoperative complications and a higher risk of gastrointestinal leak [21,22,24]. Simkens et al. [23] find an ECOG status higher than 1 (restricted in strenuous activity) is an independent risk factor for severe postoperative complications. A case series by Reuter et al. [25], only including 28 patients, does not find an association between a patient’s ECOG performance status and postoperative morbidity. An American Society of Anesthesiologists’ (ASA) status higher than 3, reflecting impaired fitness in patients, is associated with more infectious complications after HIPEC [17].

The presence of depressive symptoms preoperatively, specified as an score of >16 on the Center for Epidemiologic Studies Depression Scale (CES-D) [32] indicating the presence of depressive symptoms preoperatively, is found to be a risk factor for postoperative complications and mortality [26]. A retrospective analysis [21] shows that low health-related QoL scores on the Functional Assessment Cancer Therapy – Colorectal (FACT-C) is significantly associated with a higher risk of postoperative complications and mortality, without defining clear cutoff values. The results show the significant effect of preoperative psychological status on outcomes after HIPEC.

Patients with a recent history of smoking have an increased risk (about 4 times) of developing complications after the procedure [23]. Moreover, Ihemelandu et al. [21] show that a positive smoking history is associated with higher postoperative mortality.

### 3.2. Preoperative modifiable factors influencing postoperative LOS

The mean LOS in patients after HIPEC surgery is 16 days (27). Characteristics and results of 3 cohort studies that identified factors associated with an increased length of stay after HIPEC are shown in Table 2.

A significant effect of preoperative SGA nutritional status on LOS is demonstrated. Results of a cohort study suggest that the mean LOS is significantly longer in malnourished patients as compared to well-nourished patients [20,27]. Reece et al. conclude that for each grade of worsening malnutrition, LOS increased by an average of almost 8 days [20]. Vashi et al. [27] even have found that LOS increases by an average of 13 days if patients are categorized into the severely malnourished group (SGA-C preoperatively [27]).

A retrospective cohort study by Kubi et al. [28] shows that patients with ASA score 4 and with a positive smoking history are at higher risk to be discharged to a destination other than home (non-home discharge (NHD)), including an acute rehabilitation facility, a nursing facility or a hospice.

### 3.3. Overall survival

Median overall survival of patients undergoing HIPEC for peritoneal carcinomatosis from colorectal cancer is approximately 32 months with a range of 16–51. Five-year survival ranges from 22% to 51% [33]. Small studies in patients with peritoneal carcinomatosis from any origin showed a median overall survival of 18 months [27] and a five-year survival rate of 55% [34].

Table 3 summarizes the characteristics and findings of 4 studies that determine preoperative risk factors for decreased overall survival in patients undergoing HIPEC, including modifiable nutritional, physical and psychological factors.

Overall survival is affected by the preoperative nutritional status of patients undergoing HIPEC. Patients with preoperative muscle loss, defined as sarcopenia, have a significantly shorter overall survival after HIPEC [19]. Moreover, Vashi et al. [27] conclude that the median survival in well-nourished patients (SGA-A) is 12 months longer as compared to malnourished patients (SGA-B or SGA-C).

Two studies show that a higher baseline ECOG (also known as World Health Organization (WHO)) performance status, indicating a poor physical status, is a predictive factor of lower survival rates after HIPEC [29,30]. With every grade of worsening on the ECOG performance status, the risk for non-survival within 24 months after HIPEC increases with 75% [29].

The importance of preoperative QoL in patients undergoing HIPEC is demonstrated by Dodson et al. [29]. Their results show that higher baseline health-related QoL scores and physical well-being scores are associated with improved survival rates within 2 years after surgery.

A summary of found preoperative factors and their cut off values affecting postoperative outcomes, including postoperative complications, mortality, length of stay and overall survival, is given in Table 4.

### 4. Discussion

Since multiple studies show a positive effect of prehabilitation on postoperative outcomes in patients undergoing abdominal surgery [11], introducing such a program seems to be a logical step to improve complication rates, mortality and QoL after HIPEC. However, this scoping review demonstrates that no research has been published on the effect of prehabilitation programs in patients undergoing this complex type of surgery. The selected studies from the literature search do not answer the primary research question, but we were able to identify modifiable factors that are associated with poor postoperative outcomes and that could be targeted by prehabilitation.

Malnourishment is a common problem in patients with peritoneal carcinomatosis and is a result of both increased resting metabolism (tumor growth and chronic inflammation) and decreased caloric intake (gastro-intestinal complaints), the so-called cachexia-anorexia syndrome [35]. As well as in patients undergoing colorectal surgery [36], poor nutritional status seems to be a risk factor for higher morbidity, higher mortality, prolonged LOS and decreased overall survival after HIPEC. An effect of a preoperative nutritional intervention on improved recovery after colorectal cancer surgery has not been identified yet [37], but studies determine that a nutritional intervention as a component of multimodal prehabilitation improves functional recovery after abdominal surgery [12,38]. Since up to 45% of peritoneal carcinomatosis patients are malnourished [27], identification and management of malnutrition seems to be an important starting point of
Table 1
Summary of the characteristics and findings of studies identifying factors associated with higher postoperative complications and mortality after HIPEC.

| Author                 | Year of publication | Study type       | N (M/F) | Gender | Mean age in years | Follow-up | Prognostic factors                                                                                                                                                                                                 | Outcomes                                                                                                                                          | Findings                                                                                       |
|------------------------|---------------------|------------------|---------|--------|------------------|-----------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
| Cardi et al.           | 2019                | Retrospective    | 200     | 43/157 | 61.3 (32 – 75)   | 30 days   | Age, sex, comorbidities, SGA score, ECOG performance status, ASA score                                                                                                                                          | Postoperative complications                                                                                                                     | High preoperative ASA score (ASA>3, p = 0.0072) and poor nutritional status (SGA-B and SGA-C versus SGA-A, p = 0.0422) are independent variables significantly linked with postoperative infectious complications |
| Van Vugt et al.        | 2015                | Prospective      | 206     | 100/106| 54.4 (±13.4)     | 0.9 – 95.2| Age, sex, preoperative skeletal L3 muscle index                                                                                                                                                                   | Postoperative complications (Clavien-Dindo grade 3–5)                                                                                           | A lower L3 muscle index is independently associated with the risk of severe postoperative complications (OR 0.93, 95% CI [0.87–0.99], p = 0.018) |
| Agalar et al.          | 2020                | Longitudinal     | 56      | 23/42  | 55.4 (±12.8)     | 30 days   | Age, sex, BMI, BSA, preoperative sarcopenia                                                                                                                                                                    | Postoperative complications, mortality, overall survival                                                                                       | The presence of preoperative sarcopenia was associated with higher likelihood of postoperative complications (OR 0.047 versus 0.356, p = 0.015), higher mortality (90.0% versus 55.6%, p = 0.010), and shorter overall survival (17.7 versus 37.9 months, p = 0.005) |
| Reece et al.           | 2019                | Prospective      | 102     | 49/53  | 53.4 (±11)       | 30 days   | Age, sex, race, BMI, comorbidities, ECOG performance status, preoperative health-related QoL, smoking history                                                                                           | 30 days postoperative complications                                                                                                          | Poor ECOG performance status (OR 6.1, 90% CI [1.1–19.9], p = 0.002), low preoperative emotional well-being (OR 0.7, 90% CI [0.6–0.9], p = 0.004) and low FACT-G score (OR 1.1, 90% CI [1.0–1.2], p = 0.04) are significantly associated with 30 days postoperative complications. Positive smoking history (OR 3.3, 90% CI [1.5–7.5], p = 0.003) and low preoperative QoL (OR 0.9, 90% CI [0.8–0.9], p = 0.03) are associated with 30 days postoperative mortality |
| Ihemelandu et al.      | 2013                | Prospective      | 387     | 173/214| 54 (±6)          | 30 days   | Age, sex, race, BMI, comorbidities, ECOG performance status, preoperative healthcare-related QoL, smoking history                                                                                       | 30 days postoperative complications                                                                                                          | Poor ECOG performance status (OR 6.1, 90% CI [1.1–19.9], p = 0.002), low preoperative emotional well-being (OR 0.7, 90% CI [0.6–0.9], p = 0.004) and low FACT-G score (OR 1.1, 90% CI [1.0–1.2], p = 0.04) are significantly associated with 30 days postoperative complications. Positive smoking history (OR 3.3, 90% CI [1.5–7.5], p = 0.003) and low preoperative QoL (OR 0.9, 90% CI [0.8–0.9], p = 0.03) are associated with 30 days postoperative mortality |
| Baratti et al.         | 2012                | Prospective      | 426     | 157/296| 54 (44–64)       | 30 days   | Age, sex, ECOG performance status                                                                                                                                                                               | 30 days postoperative complications                                                                                                          | ECOG performance status higher than 0 is an independent predictor of complications (OR 2.028, 95% CI [1.137–3.621], p = 0.017) |
| Simkens et al.         | 2016                | Retrospective    | 211     | 102/109| 62.9 (24.4–80.7) | 90 days   | Age, sex, BMI, ASA score, ECOG performance status, alcohol consumption, smoking history, comorbidities                                                                                                                                 | 90 days postoperative complications (Clavien-Dindo grade 3–5)                                                                                | A positive recent history of smoking (OR 3.99, 95% CI [1.75–9.10], p = 0.001) and an ECOG performance status higher than 1 (OR 2.89, 95% CI [1.31–6.35], p = 0.010) are independent risk factors for postoperative complications (Clavien-Dindo grade 3–5) |
| Chouliaris et al.      | 2017                | Prospective      | 1270    | 579/689| 54 (39–80)       | 30 days   | Age, sex, ECOG performance status, comorbidities                                                                                                                                                                 | Postoperative gastrointestinal leak                                                                                                           | A predictor of gastrointestinal leak was ECOG functional status (ECOG 1 versus 0; OR 2.12, 95% CI [1.21–3.74], p = 0.009; ECOG 2 versus 0: OR 2.90, 95% CI [1.42–5.91], p = 0.004) |                                                                                           |
| Reuter et al.          | 2008                | Case series      | 28      |       | 52 (39–80)       | 30 days   | ECOG performance status                                                                                                                                                                                       | 30 days postoperative complications                                                                                                          | No significant results reported                                                                                                                          |
| Low et al.             | 2016                | Prospective      | 98      | 54/44  | 54.83 (18–78)    | 30 days   | Age, race, sex, BMI, ASA score, depressive symptoms                                                                                                                                                             | 30 days postoperative complications, readmission within 30 days, overall survival                                                               | The presence of clinically significant depressive symptoms is significantly associated with 30 days postoperative complications (OR 4.26, 95% CI [1.21–14.99], p = 0.011) and readmission within 30 days (OR 4.59, 95% CI [1.32–18.14], p = 0.024) |                                                                                           |

N – number of patients included, M – male, F – female, SGA – Subjective Global Assessment, ECOG – Eastern Cooperative Oncology Group, ASA – American Society of Anaesthesiologists, ECOG – Eastern Cooperative Oncology Group, BMI – Body Mass Index, BSA – Body Surface Area, LOS – length of stay, QoL – Quality of Life, FACT-G – Functional Assessment of Cancer Therapy-General.
The mean LOS for patients in the preoperative SGA-C group is significantly longer than the mean LOS for those in the SGA-A and SGA-B groups (28.8 versus 15.0 and 15.2 days respectively, \( p = 0.02 \)). Well-nourished patients (SGA-A) have a median survival of 22.4 months (95% CI [18.7–26.1]), while malnourished patients (SGA-B and SGA-C) have a median survival of 10.4 months (95% CI [5.2–15.7]); the difference being statistically significant (log rank \( p = 0.006 \)). Infectious complications were more common in malnourished patients as compared to well-nourished patients (47% vs 25%, \( p = 0.025 \)). Malnutrition is significantly associated with LOS, with LOS 7.65 days longer in malnourished patients (95% CI [1.67–13.62, \( p = 0.013 \]).

### Table 2
Summary of the characteristics and findings of studies identifying factors associated with LOS after HIPEC.

| Author            | Year of publication | Study type       | N   | Gender (M/F) | Mean age in years | Follow-up | Prognostic factors                                      | Outcomes                                      | Findings                                                                 |
|-------------------|---------------------|------------------|-----|--------------|-------------------|-----------|-------------------------------------------------------|-----------------------------------------------|------------------------------------------------------------------------|
| Vashi et al. [27] | 2019 Retrospective  | 60               | 19/41 | 50.3 (21.4–69.1) | 15.1 months (19–37.8) | Age, sex, SGA nutritional status | LOS, postoperative complications, postoperative ECOG performance status, survival | The mean LOS for patients in the preoperative SGA-C group is significantly longer than the mean LOS for those in the SGA-A and SGA-B groups (28.8 versus 15.0 and 15.2 days respectively, \( p = 0.02 \)). Well-nourished patients (SGA-A) have a median survival of 22.4 months (95% CI [18.7–26.1]), while malnourished patients (SGA-B and SGA-C) have a median survival of 10.4 months (95% CI [5.2–15.7]); the difference being statistically significant (log rank \( p = 0.006 \)). Infectious complications were more common in malnourished patients as compared to well-nourished patients (47% vs 25%, \( p = 0.025 \)). Malnutrition is significantly associated with LOS, with LOS 7.65 days longer in malnourished patients (95% CI [1.67–13.62, \( p = 0.013 \]). Significant predictors of NHD identified were an ASA score of 4 (OR, 2.87, 95% CI [1.21–6.83]), \( p = 0.017 \) and smoking history (OR, 3.22; 95% CI [1.70–6.12], \( p < 0.001 \). |
| Reece et al. [20] | 2020 Prospective    | 106              | 49/53 | 55 (±12.8) | 30 days | Age, sex, preoperative nutritional status | LOS, 30 days postoperative complications (Clavien-Dindo grade 3–5) |                                                              |                                                                 |
| Kubi et al. [28]  | 2020 Retrospective  | 1593             | 640/883 | 55.14 (±12.1) | 30 days | Age, sex, BMI, ASA, ECOG performance status, smoking history | NHD |                                                                 |                                                                 |

N = number of patients included, M = male, F = female, SGA = Subjective Global, LOS = length of stay, Assessment, ECOG = Eastern Cooperative Oncology Group, CI = Confidence Interval, BMI = Body Mass Index, NHD = Non-Home Discharge, ASA = American Society of Anaesthesiologists’, OR = Odds Ratio.

### Table 3
Summary of the characteristics and findings of studies identifying factors associated with overall survival after HIPEC.

| Author            | Year of publication | Study type       | N   | Gender (M/F) | Mean age in years | Follow-up | Prognostic factors                                      | Outcomes                                      | Findings                                                                 |
|-------------------|---------------------|------------------|-----|--------------|-------------------|-----------|-------------------------------------------------------|-----------------------------------------------|------------------------------------------------------------------------|
| Agalar et al. [19]| 2020 Longitudinal  | 56               | 23/42 | 54.4 (±13.4) | 30 months (0.9–95.2) | Age, sex, BMI, BSA, preoperative sarcopenia | Overall survival, postoperative complications, mortality | The presence of preoperative sarcopenia was associated with shorter overall survival (17.7 versus 37.9 months, \( p = 0.005 \)), higher likelihood of postoperative complications (70.0% versus 35.6%, \( p = 0.015 \) and higher mortality (90.0% versus 55.6%, \( p = 0.010 \)). Well-nourished patients (SGA-A) have a median survival of 22.4 months (95% CI [18.7–26.1]); the difference being statistically significant (log rank \( p = 0.006 \)). The mean LOS for patients in the preoperative SGA-C group is significantly longer than the mean LOS for those in the SGA-A and SGA-B groups (28.8 versus 15.0 and 15.2 days respectively, \( p = 0.02 \)). |
| Vashi et al. [27] | 2013 Retrospective  | 60               | 19/41 | 50.3 (21.4–69.1) | 15.1 months (1.9–37.8) | Age, sex, SGA nutritional status | Survival, LOS, postoperative complications, postoperative ECOG performance status |                                                              |                                                                 |
| Dodson et al. [29]| 2016 Prospective    | 598/322          | 276/322 | 53.3 (±12.1) | 24 months | Preoperative QoL survey (36-SF, FACT-G, FACT-C, CES-D) | Overall survival | Higher baseline FACT-G score (HR 0.92, 95% CI [0.09–0.96], \( p < 0.001 \), FACT-C score (HR 0.73, 95% CI [0.65–0.83], \( p < 0.001 \), physical well-being (HR 0.71, 95% CI [0.64–0.78], \( p < 0.001 \), and 36-SF score (HR 0.88, 95% CI [0.83–0.92], \( p < 0.001 \) are associated with improved overall survival. Higher baseline ECOG performance score is associated with worse survival (HR 1.74, 95% CI [1.50–2.01], \( p < 0.0001 \). WHO performance status 2 and 3 significantly correlates with lower overall survival than WHO performance status 1 (HR = 3.5, 95% CI [1.29–9.98], \( p = 0.014 \). |
| Desantis et al. [30]| 2014 Retrospective | 401/320          | 81/320 | 56.9 (22–75) |                | Age, sex, BMI, WHO performance status | Overall survival, mortality (Clavien-Dindo grade 3–5), disease-free survival |                                                              |                                                                 |
prehabilitation prior to HIPEC.

Based on small, underpowered and high risk of bias studies, performance status as a predictive factor of developing complications and of remaining longer hospitalized after HIPEC seems rational. However, more solid proof is needed. The overall survival after HIPEC was found to be worse in patients with impaired physical health. In line with the association between performance status and postoperative outcomes for colorectal surgery [36], preoperative physical support seems promising and the effect of preoperative physical support prior to colorectal surgery has already been investigated in multiple studies. Overall data, summarized in a systematic review by Bolshinsky et al., support that exercise prehabilitation is an effective way to improve preoperative performance status [39].

In general, patients with a recent positive smoking history have a higher risk of postoperative complications and mortality, which is also seen in patients undergoing colorectal surgery [40]. Research demonstrates that preoperative smoking cessation interventions reduce postoperative morbidity [41], which suggest that smoking cessation support should be a part of prehabilitation in patients undergoing HIPEC.

It is well known that patients undergoing surgical treatment experience anxiety preoperatively concerning the procedure, its outcome and their postoperative recovery [42]. This interferes with postoperative outcomes [43]. Lower health-related QoL is associated with higher complication rates, prolonged LOS and worse overall survival in patients undergoing HIPEC. Psychological support can reduce anxiety and stress pre- and perioperatively [43,44] and should therefore be incorporated into prehabilitation programs prior to HIPEC.

Whilst interpreting above mentioned results, it should be kept in mind that included studies in this review are heterogeneous and that it is likely that not all studies reporting on modifiable risk factors for poor postoperative outcomes in patients undergoing HIPEC were included in the qualitative synthesis, since this is not the primary research question of this review. However, the results are in line with studies that report on preoperative factors associated with impaired recovery after colorectal surgery [36]. It is not very likely that including more studies reporting on this topic will show contradictory results.

By identifying and evaluating above mentioned risk factors, this review shows the importance of targeting multifactorial factors during prehabilitation in HIPEC. Therefore, programs to optimize a patient undergoing HIPEC preoperatively should be focusing on both nutritional status, performance status, health-related quality of life and smoking and thus be multimodal.

A patient’s preoperative nutritional status and performance status is also affected by the extent of peritoneal carcinomatosis, which in its turn influences the complexity of the surgical procedure. Cytoreduction in patients with extensive peritoneal metastases consists of more complex multi-organ resections and therefore leads to a higher risk of postoperative complications. It is important to realize that prehabilitation will not avert the progress of the disease and thus the magnitude of the surgical procedure. However, improving nutritional and performance status as best as possible by prehabilitation, regardless the extent of peritoneal carcinomatosis, might minimize the risk of complications associated with complex surgery.

Such multimodal prehabilitation programs have already been well-investigated in colorectal surgery. Recently, several randomized controlled trials on the effect of prehabilitation on clinical outcomes in patients with colorectal cancer have been published [11,45,46]. These studies, including 533 patients, show a significant reduction on postoperative complications (up to 51%) and length of hospital stay (-1 day) in patients undergoing a prehabilitation program prior to surgery. Since the modifiable risk factors found in this review correspond to independent risk factors associated with postoperative complications and poor outcomes in colorectal surgery [36], and the positive effect in patients with colorectal cancer is already well-known, it could be hypothesized that similar effects of prehabilitation will be seen in patients undergoing HIPEC.

Results from this review stimulate initiation of well-conducted research to further explore the true value of prehabilitation programs in patients undergoing HIPEC, and contribute to our gut-feeling that the fitter the patient is prior to surgery, the fitter the patient will be after. Scientific support is therefore needed.
5. Conclusion

HIPEC is a complex procedure associated with a high risk of complications, leading to increased mortality rates and impaired QoL. Regarding the positive effects of prehabilitation in colorectal surgery, introducing such a program to optimize preoperative functional capacity might be a promising way to improve recovery after HIPEC. Unfortunately, trials on the effect of prehabilitation prior to HIPEC have not been performed yet. This review demonstrates that preoperative modifiable risk factors for poor outcomes in patients undergoing HIPEC are multifactorial. Prehabilitation programs prior to HIPEC should therefore be multimodal and should combine nutritional support, psychical exercise, psychological support and smoking cessation, but also new factors should be researched. The effect of such multimodal prehabilitation programs in patients undergoing HIPEC should be investigated in future trials.

CRediT authorship contribution statement

D. Strijker: Conceptualization, Methodology, Investigation, Formal analysis, Writing — original draft. W.J.H.J. Meijerink: Conceptualization, Resources, Writing — review & editing. A.J.A. Bremers: Resources, Writing — review & editing. P. de Reuver: Resources, Writing — review & editing. J.H.M. van Laarhoven: Resources, Writing — review & editing. B. van den Heuvel: Conceptualization, Methodology, Investigation, Formal analysis, Writing — original draft, Writing — review & editing. Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.10.006.

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