August 9, 2022

Dear Editor,

I would like to submit the revised manuscript 77629 entitled " **Quality of Life and Symptom Distress after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy** " in the **World Journal of Clinical Cases** as an original article. We greatly appreciate the reviewers' comments and have made changes according to their precious suggestions. We have herein revised the manuscript according to the comments point by point and highlighted the changes in the revised manuscript. The mention page number below is cited according to those in the *marked copy*.

#Response to Reviewer 1

1. Please provide the flow diagram of patient enrollment

Response 1. Thanks for the comment. As suggested, we have provided a new flowchart entitled "Figure 1" and figure legend in the result section (p.14 and p.33).

2. This is a prospective cohort study, the sample size calculating process should be provided.

Response 2. The total sample size was calculated using Gpower version 3.1. The effect size was determined to be 0.25. The study power and alpha value were set at 80% and 0.05, respectively. Based on these inputs, a minimum sample of 44 subjects is required. These have been added in the Statistical Analysis section. (Line 248)

Original	Revised
Statistical Analysis Demographic data and scale scores were reported with descriptive statistics, including number, percentage, mean (standard deviation) and median (range).	***Statistical Analysis*** The total sample size was calculated using Gpower version 3.1. The effect size was determined to be 0.25. The study power and alpha value were set at 80% and 0.05, respectively. Based on these inputs, a minimum sample of 44 subjects is required. Demographic data and scale scores were reported with descriptive statistics, including number,

	percentage, mean (standard deviation) and median (range).

3. The CRS/HIPEC indication for this study were: (1) curative intent of peritoneal metastases from primary or recurrent malignancies with peritoneal metastases; (2) palliation to control ascites; and (3) adjuvant treatment for the prophylaxis of suspicious T4 disease from gastric cancer and colorectal cancer or tumor rupture during surgery. There were too many potential influencing factors like primary disease, previous surgery, patients' systemic status might correlate to the results of this study, especially for the relatively small sample size in this study, the bias might be enlarged.

Response 3. Thanks for the comment. Due to the small sample size in this study, we were not able to provide subgroup analysis for patients with different cancer type and preoperative conditions. Therefore, we have included a short sentence in the limitation section in the original manuscript as "A minor limitation was that this study included patients with several types of cancer". To further address this issue, we have provide additional information. The revised paragraph were as below:

"A minor limitation was that this study included patients with different types of cancer and cancer surgery. Moreover, subgroup analysis for patients with different treatment intend and preoperative status were not performed due to small sample size."(Line 385-388)

Original	Revised
A minor limitation was that this study included patients with several types of cancer.	A minor limitation was that this study included patients with different types of cancer and cancer surgery. Moreover, subgroup analysis for patients with different treatment intend and preoperative status were not performed due to small sample size.

#Response to Reviewer 2

1. Congratulations to the authors for the choice of topic and implementation of study. This study investigates the quality of life (QoL) and symptom distress after cytoreductive surgery and hyperthermic intraperitoneal chemotherapy with currently used chemotherapeutic agents and operative

techniques. QoL and symptom severity improved or returned to baseline in most categories within 3 months after CRS/HIPEC. Our findings can help with preoperative consultation and perioperative care.

Response: We thank the reviewer for the positive comments on our manuscript.

#Response to Reviewer 3

1. What does "our findings" in conclusion on P.18 indicate? Are they "age ≥ 55 years in emotional functioning at S2 and ECOG performance status in preoperative physical functioning and role functioning at S3" on P.14? Are they that "QoL and symptom severity improved or returned to baseline in most categories within three months after CRS / HIPEC" ?

Response 1. Thanks for the comment for making our conclusion more precise. We have revised the conclusion section according to the suggestions. (Line 401-404)

Original	Revised
In conclusion, our findings may help MDT members to identify patients undergoing CRC/HIPEC who are at high risk of perioperative symptom distress and decline in QoL, and give these patients adequate counseling and perioperative support.	Our findings of younger age and poor preoperative ECOG performance status may help MDT members to identify patients undergoing CRC/HIPEC who are at high risk of perioperative symptom distress and decline in QoL. Patient counseling and peri-operative support may be provided accordingly.

2. Do the authors conclude that QoL and symptom distress after CRS/HIPEC are recovered in 3 months in Taiwan, similar to the results of previous studies? If so, I cannot understand from which result they consider that the current study emphasizes the importance of perioperative mental health considerations in cancer patients receiving aggressive treatment on P.18.

Response 2. Thanks for the comment. Several studies have reported a QoL decline in patient following surgery with subsequent recovery in 3 to 6 months. However, studies targeting Asia populations were limited and have reported a longer QoL recovery time of 6-18 months after CRS/HIPEC (Introduction, Line 124-128, reference 2,3,5,6,12). Our study showed that QoL

and symptom severity could recovery in 3 months following CRS/HIPEC in Taiwanese patients under multidisciplinary team care, which agreed with previous study results targeting Western populations. Our findings support the importance of MDT approach and encourage effective teamwork for CRS/HIPEC care. These have been added in the conclusion section (Line 404-406).

Original	Revised
The current study emphasizes the importance of perioperative mental health considerations in cancer patients receiving aggressive treatment.	QoL and symptom severity convalescing after three months reiterate the importance of the MDT approaches towards an effective teamwork for CRS/HIPEC care.

3. The authors describe that the risk factors associated with a perioperative decline in QoL were an age <55 years old and poor ECOG performance (ECOG = 2) on P.15. What do you think is the reason why younger patients under 55 years old had a higher decrease in QoL?

Response 3. Thanks for the comment. This study identified younger age (<55 years old) as a risk factor for poorer perioperative decline in QoL and similar results have been reported by previous studies (Health Qual Life Outcomes. 2013 Mar 14;11:46.; Indian J Palliat Care. 2019 Jul-Sep;25(3):414-420.). Younger patients may have greater socioeconomic stress, lower incomes, and weak family supports, and these would contribute to the feeling of hopelessness and these may result in a low QoL (Indian J Palliat Care. 2019 Jul-Sep;25(3):414-420). Our preliminary finding was younger age <55 years have poorer emotional functioning at early post-operative visit (S2). Although, further analyses are needed to include these factors in the prediction models and assess their roles in influencing QoL.

We have added this discussion in Line 364-371 and added reference 24, and 25.

4. A feature of this study is the high proportion of patients with gastric cancer. Were there any differences in primary resection during CRS between gastric cancer and colorectal cancer? Did the differences influence on QoL?

Response 4. Thanks for the comment. The major differences in primary resection between gastric cancer and colon cancer are gastrectomy in gastric

cancer which influence the postoperative nutrition status and the possibility of stoma after intestine resection in colon cancer. These differences would influence the QoL. However, lack these data assessment was the limitation in this study. We have revised the limitation according to the comment (Line 385-388)

Original	Revised
A minor limitation was that this study included patients with several types of cancer. However, patients with peritoneal carcinomatosis may have similar problems and cytoreduction principles regardless of cancer types.	A minor limitation was that this study included patients with different types of cancer and cancer surgery. Moreover, subgroup analysis for patients with different treatment intend and preoperative status were not performed due to small sample size.

5. The advantage of this study is that it is a prospective study. The HIPEC time was prescribed as 60-90 minutes according to the regimen, but it was 75.9% of ≤60min in Table 1. Does the result mean a violation of the protocol?

Response 5. Thanks for pointing out the error. In this study, HIPEC regimens can be categorized into three group: cisplatin-based, mitomycin C and mitomycin C plus doxorubicin. The HIPEC perfusion lasted for approximately 60, 90 and 60 minutes for the cisplatin-based, mitomycin C and mitomycin C plus doxorubicin groups, respectively. We have revised the item of "Duration of HIPEC" in Table 1 using two sub-items – 60 mins and 90 mins.

We highly appreciate the comments from the reviewers.

Thank you very much for your kind consideration.

Very sincerely,

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Observational Study

Quality of Life and Symptom Distress after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

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conceptualization, methodology, data curation, and writing—original draft preparation and editing; Lin MH and Wang YF were responsible for the data analysis and software; Huang TH, Chen VCH, Lee LW, Hsieh MC, Huang WS were responsible for resources and supervision; Wang YF received the grants.

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Abstract

BACKGROUND

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) for peritoneal surface malignancy can effectively control the disease, however it is also associated with adverse effects which may affect quality of life (QoL).

AIM

To investigate early perioperative QoL after CRS/HIPEC, which has not been discussed in Taiwan.

METHODS

This single institution, observational cohort study enrolled patients who received CRS/HIPEC. We assessed QoL using the Taiwanese version of the MD Anderson Symptom Inventory (MDASI-T) and European Organization Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30). Participants completed the questionnaires before CRS/HIPEC (S1), at the first outpatient follow-up (S2), and 3 months after CRS/HIPEC (S3).

RESULTS

Fifty-eight patients were analyzed. There was no significant perioperative difference in global health status. Significant changes in physical and role functioning scores decreased at S2, and fatigue and pain scores increased at S2 but returned to baseline at S3. Multiple regression analysis showed that age and performance status were significantly correlated with QoL. In the MDASI-T questionnaire, distress/feeling upset and lack of appetite had the highest scores at S1, compared to fatigue and distress/feeling upset at S2, and fatigue and lack of appetite at S3. The leading interference items were working at S1 and S2 and activity at S3. MDASI-T scores were significantly negatively correlated with the EORTC QLQ-C30 results.

CONCLUSION

QoL and symptom severity improved or returned to baseline in most categories within 3 months after CRS/HIPEC. Our findings can help with preoperative consultation and perioperative care.

Key words: Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Peritoneal carcinomatosis; Quality of life; Symptom distress;

Perioperative care

Core tip: Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) for peritoneal surface malignancy is associated with adverse effects which may affect quality of life (QoL). We aimed to investigate QoL after CRS/HIPEC, which has not been discussed in Taiwan. In this study, we prospectively enrolled patients in our single-center data between 2018 and 2021. Our data showed that age and performance status were significantly correlated with QoL. QoL and symptom severity improved or returned to baseline in most categories within 3 months after CRS/HIPEC. Our findings can help with preoperative consultation and perioperative care.

INTRODUCTION

Peritoneal surface malignancy (PSM) is the spread of cancer cells inside the abdominal cavity, especially over the peritoneum, the membrane that covers the abdominal cavity. PSM was considered to be a terminal stage of cancer, and hence patients with PSM were often treated with palliative systemic therapies or supportive care [1-3]. PSM may cause abdominal distension, ascites, malnutrition, cachexia, and intestinal obstruction, which in turn can cause physical and mental discomfort, significantly reducing the quality of life (QoL) and shortening survival [1, 4-6].

However, cytoreductive surgery (CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has become a treatment option beyond palliative treatment for patients with PSM [1, 7]. Although CRS/HIPEC can prolong survival, it can also cause adverse effects such as postoperative ileus, wound infection, intra-abdominal abscess, bleeding, symptomatic pleural effusion, anastomotic leakage, and renal damage [7-10]. Although some of these adverse effects are short term, some may persist for a long time. The potential survival benefit must therefore be weighed against a possible reduction in QoL associated with the procedure and its complications. In addition, uncertainty of the illness and facing aggressive treatment may affect the emotional well-

being of the patient [11]. Therefore, the QoL after CRS/HIPEC is an important issue [4, 5].

In recent years, several Western studies have investigated the QoL after CRS/HIPEC. In a systematic review, Shan et al. reported that CRS/HIPEC for PSM could confer small to medium benefits for health-related QoL. However, the authors concluded that the results should be interpreted with caution due to the small studies and varying follow-up duration [4]. Several studies have reported that the QoL of patients usually declines after surgery, but then recovers to baseline and improves in 3 to 6 months [2, 3, 5, 6, 12]. However, most of these reported were retrospective QoL or clinical data studies. In addition, only two studies on Asian patients have been reported, and although they reported that QoL would recover in 6-18 months after CRS/HIPEC, they both enrolled a small number of patients [2, 13]. Taken together, these previous studies have all focused on the QoL 3 months or later after surgery. Investigations of perioperative QoL and symptom severity after CRS/HIPEC are limited. However, perioperative psychological distress and changes in QoL are crucial, because they may decrease treatment acceptance by the patients and affect perioperative care by the physicians.

HIPEC has been reimbursed by the National Health Insurance system since

2019 in Taiwan, and the number of patients undergoing CRS/HIPEC has gradually increased. Consequently, the impact on QoL of this treatment has also gradually become more important due to socio-economic considerations. Contemporary cancer treatment focuses on both survival and the relief of symptoms to improve function and the QoL of patients. Thus, we conducted this prospective study to investigate changes in QoL in the perioperative stage after CRS/HIPEC, and explore the factors associated with these changes.

MATERIALS AND METHODS

Study Design

This was a prospective, single institution, cohort study in Taiwan. The inclusion criteria were: (1) patients who planned to receive CRS/HIPEC at Chang Gung Memorial Hospital in Chiayi from September 1, 2018 to February 28, 2021; and (2) patients aged ≥ 20 years. The exclusion criteria were: (1) patients who had psychiatric disorders; (2) patients unable to understand the questionnaires; or (3) patients who were not willing to complete all questionnaires. The participants were asked to complete the questionnaires at three time points (first visit, before CRS/HIPEC; second visit, the first outpatient follow-up after CRS/HIPEC; and third visit, the outpatient visit 3 months after CRS/HIPEC).

158 We defined the first visit as S1, second visit as S2, and third visit as S3. Data
159 were collected using the Taiwan version of the MD Anderson Symptom
160 Inventory (MDASI-T), and Traditional Chinese version of the Core Quality of
161 Life Questionnaire compiled by the European Organization for Research and
162 Treatment of Cancer (EORTC QLQ-C30). All questionnaires were completed in
163 face-to-face interviews with the researchers and patients. The study was
164 conducted according to the guidelines of the Declaration of Helsinki and
165 approved by the Institutional Review Board of Chang Gung Medical Hospital
166 (No. 201800726B0). The informed consent was obtained by all participants.
167
168 ***Survey Measures***
169 ***MD Anderson Symptom Inventory***
170 Symptom data were obtained using the MDASI-T [14], which contains 13 core
171 symptom severity items and six interference items. Symptoms (pain,
172 fatigue/tiredness, nausea, disturbed sleep, distress, shortness of breath,
173 difficulty remembering, lack of appetite, drowsiness, dry mouth, sadness,
174 vomiting, and numbness/tingling) were rated at their worst in the previous 24
175 hours on a 0–10 scale, with 0 representing "not present" and 10 representing
176 "as bad as you can imagine." The patients also rated the degree to which the

177 symptoms interfered with various aspects of life during the past 24 hours. Each
178 interference item (general activity, mood, work [including both work outside
179 the home and housework], relations with other people, walking ability, and
180 enjoyment of life) was rated on a 0–10 scale, with 0 representing "did not
181 interfere" and 10 representing "interfered completely" [15].

182 ***QoL Questionnaire***

183 The health-related QoL was assessed using the EORTC QLQ-C30 [16]. The
184 questionnaire contains a total of 30 questions and covers five functional scales
185 (physical, role, cognitive, emotional, and social function), three symptom scales
186 (fatigue, pain, and vomiting), six symptom single item scales (dyspnea,
187 insomnia, loss of appetite, constipation, diarrhea, and financial status), and a
188 self-perceived global health status scale. Except for questions 29 and 30, which
189 are answered on a scale from 1 to 7 points, the options for the other questions
190 range from 1 ("Not at all") to 4 ("Very much"). The scores are then converted
191 into percent scores according to the questionnaire instruction manual. In the
192 self-perceived global health status score and functional score, the higher the
193 score, the better the patient's function or QoL. While in the symptom score and
194 single selection, the higher the score, the more severe the symptoms, meaning
195 poor QoL.

196

197 ***CRS/HIPEC Procedure***

198 All participants were reviewed by a multidisciplinary team (MDT) committee.
199 The HIPEC procedure was indicated for: (1) curative intent of peritoneal
200 metastases from primary or recurrent malignancies with peritoneal metastases;
201 (2) palliation to control ascites; and (3) adjuvant treatment for the prophylaxis
202 of suspicious T4 disease from gastric cancer and colorectal cancer or tumor
203 rupture during surgery. Before treatment, we evaluated the patient's
204 comprehensive medical history, physical examination, blood test, and imaging.
205 All procedures were performed by the same HIPEC team at Chang Gung
206 Memorial Hospital, Chiayi, using a unified technique. The team performed
207 CRS to remove all visible peritoneal lesions, then used the closed HIPEC
208 technique with a Performer™ HT system (RanD Biotech, Medolla, Italy). The
209 perfusate was given at a dose of 2 L/m2 of body surface and temperature of 41-
210 43°C for 60-90 minutes according to the regimen [17]. The chemotherapeutic
211 agents used included mitomycin, cisplatin, and doxorubicin.

212

213 ***Clinical Data Collection***

214 Data on the patients' characteristics, operative details, postoperative outcomes,

215 and pathology were evaluated by the MDT committee. The prospectively
216 collected data of the patients included demographics, pre-existing co-
217 morbidities (diabetes, hypertension, and hepatitis), Eastern Cooperative
218 Oncology Group (ECOG) performance status, cancer type/disease status
219 (primary or recurrence, histology type and grade, and peritoneal
220 carcinomatosis index (PCI)), CRS/HIPEC parameters (chemotherapy regimen,
221 duration, and completeness cytoreduction (CC) score [18], grade of
222 postoperative complications according to the National Cancer Institute –
223 Common Terminology Criteria for Adverse Events (NCI-CTCAE) v.5.0, and
224 nutritional status according to the Patient-Generated Subjective Global
225 Assessment (PGSGA) score.
226
227 ***Statistical Analysis***
228 The total sample size was calculated using Gpower version 3.1. The effect size
229 was determined to be 0.25. The study power and alpha value were set at 80%
230 and 0.05, respectively. Based on these inputs, a minimum sample of 44 subjects
231 is required. Demographic data and scale scores were reported with descriptive
232 statistics, including number, percentage, mean (standard deviation) and
233 median (range). The student's t-test, one-way analysis of variance (ANOVA),

and Pearson's correlation coefficients were used to compare differences and correlations, respectively. Multiple regression analysis was used for inferential statistics. A two-sided *P* value of < 0.05 was considered to be statistically significant. All analyses were performed using SAS version 9.4 (SAS Inc., Cary, NC).

RESULTS

Patients

During the study period, 79 patients were screened preoperatively for enrollment into the study. However, 17 patients canceled the CRS/HIPEC procedure intraoperatively after the laparoscopic examination (13 because the disease was too extensive and cytoreduction could not be completed, and four who did not have PSM and refused to receive prophylactic HIPEC). After CRS/HIPEC, four patients withdrew from the study. Therefore, a total of 58 patients completed the study and were eligible for analysis (Figure 1). However, three patients returned to their original hospitals for further salvage therapy and did not complete the third questionnaire. The basic and disease characteristics of the patients are shown in Table 1. The median (range) age of all patients was 60 (22-78) years, and the most common cancer type was gastric

253 cancer (46.6%). The median length of hospital stay was 13 days. Fifty-two
254 patients (89.7%) had postoperative complications, of which grade I
255 complications were the most common (72.4%). Forty-two patients (85.7%) had
256 a PGSGA score of A.
257
258 ***QoL and Symptoms Severity***
259 The results of the EORTC QLQ-C30 and MDASI-T questionnaires are shown in
260 Table 2. The average preoperative global health status scores at S1, S2, and S3
261 were 60.3, 56.6, and 64.4, respectively. The results showed a trend of a reduction
262 in global health status after surgery and then an improvement at S3, however
263 there was no statistical difference ($p = 0.065$). On the functional scale, there were
264 significant decreases in the physical function ($p = 0.001$) and role function ($p =$
265 0.004) scores at S2, which then recovered to the preoperative baseline level at
266 S3. In the symptom and multiple-item scales, fatigue ($p = 0.004$) and pain ($p =$
267 0.002) significantly increased at S2. The most significant improvement at S3 was
268 in dyspnea ($p = 0.041$). In the MDASI-T questionnaire, there were no significant
269 changes in the average scores for the severity of preoperative symptoms and
270 the degree of interference with life between S1, S2, and S3 (Table 2). In the
271 preoperative stage, the two symptom items with the highest scores were

distress/feeling upset (2.2±2.1) and lack of appetite (1.7±2.4). After CRS/HIPEC, the two symptom items with the highest scores were fatigue (tiredness) (2.0±1.8) and distress/feeling upset (2.0±2.1) at S2, and fatigue (tiredness) (2.0±1.6) and lack of appetite (1.7±1.8) at S3. Regarding the interference items, the items with the highest scores were working (including housework) at S1 (2.1±2.9) and S2 (2.2±3.0) and activity at S3 (1.5±1.5).

Relationships among Patient Characteristics, MDASI-T and EORTC QLQ-C30

Table 3 shows the relationships among the EORTC QLQ-C30 and its related factors using the student's t-test, one-way ANOVA, and Pearson's correlation coefficients. The severity score was significantly negatively correlated with preoperative global health status ($r = -0.48$, $p < 0.001$), emotional function ($r = -0.34$, $p < 0.01$), and cognitive function ($r = -0.54$, $p < 0.001$). The score of the degree of interference with life was significantly negatively correlated with preoperative global health status and all functional scales ($r = -0.39 \sim -0.54$, $p < 0.01$).

At S2, the physical and social function scores of the patients who were ≥55 years old were significantly higher than those of the patients who were <55

291 years old ($p < 0.05$). The symptom severity score was significantly negatively
292 correlated with role function ($r = -0.45$, $p < 0.001$), emotional function ($r = -0.49$,
293 $p < 0.001$) and social function ($r = -0.33$, $p < 0.05$). The degree of interference
294 with life scores were significantly negatively correlated with the global health
295 status and all functional scales ($r = -0.28$~ -0.63, $p < 0.05$).

296 At S3, the role function score of ≥55 years old was significantly higher than
297 those who <55 years old ($p<0.05$). The scores of global health status of patients
298 who received chemotherapy before surgery were significantly higher than
299 those who did not ($p<0.05$). The symptom severity score had a significant
300 negative correlation with role function, emotional function, cognitive function,
301 and social function ($r = -0.48$ ~ -0.72, $p<0.001$), and the degree of interference
302 with life score showed a significant negative correlation with global health
303 status, role function, emotional function, cognitive function, and social function
304 ($r = -0.67$ ~ -0.78, $p<0.001$).

305

306 ***Determinants of QoL***

307 The results of multiple regression analysis for the significantly correlated
308 variables in Table 3 are shown in Table 4. The results showed that the important
309 predictors were age ≥55 years old in emotional functioning at S2 ($\beta = -0.40$, $p <$

0.05), and ECOG performance status in preoperative physical functioning (β = 21.49, $p < 0.05$) and role functioning at S3 (β=29.63, $p<0.05$). Both the severity of symptoms and degree of interference with life in the MDASI-T were significantly correlated with QoL as measured using the EORTC QLQ-C30.

DISCUSSION

This is the first prospective study to investigate the QoL and symptoms distress after CRS/HIPEC in Taiwan. The results of this study showed that most patients had a significant decline in physical and role function scores at S2, but that they returned to the preoperative status at S3. We also found that the most serious symptoms after surgery were fatigue and pain, and that pain returned to the preoperative status 3 months after surgery. There was no significant decline in global health status after surgery. Both items in the MDASI-T were significantly negatively correlated with the EORTC QLQ-C30 results. We also found that the risk factors associated with a perioperative decline in QoL were an age <55 years old and poor ECOG performance (ECOG = 2).

Several studies have reported that patients' functional scales, especially physical and role functional scales, declined at 3 months and then returned to the baseline level at 6-9 months [1, 2, 5, 6, 19]. However, we found that the physical

329 and role function scores were lower at the first outpatient follow-up visit after
330 surgery and then recovered to the preoperative baseline scores within 3 months.
331 This result is similar to that reported by Alves et al. [12]. We hypothesize that
332 the patients may have felt a loss of role function under the care of family
333 members after surgery, and that their physical function was also limited
334 because of surgical wounds and pain. As the wounds gradually healed, their
335 daily role functions were restored and the functional scale scores gradually
336 increased.

337 In addition, the emotional and cognitive function scores of the patients in this
338 study showed a tendency to increase after CRS/HIPEC. This result is similar to
339 previous studies [1, 2, 8, 13, 20]. The reason may be due to a release of anxiety over
340 uncertainty of the surgery, and because most of the patients recognized that the
341 cancer was being well treated and that the treatment could prolong their life.
342 In addition, patients with positive emotions or optimistic personalities tend to
343 have a broader scope of cognition [21].

344 Of the symptom scales, fatigue and pain had the worst scores at the first
345 outpatient follow-up visit after surgery. These symptoms may be caused by
346 laparotomy wounds and the effects of HIPEC, and have been reported in other
347 studies [6, 22]. Chia et al. reported that other symptoms would recover in 6-12

348 months after HIPEC/CRS as well as other major surgery [2]. In this study, the
349 pain scales returned to baseline at 3 months after surgery, but the other
350 symptoms did not. In addition, 90% of the patients in this study received
351 adjuvant chemotherapy which may have begun within 3 months
352 postoperatively, and this may also have contributed to the persistent symptoms.
353 Previous studies have reported that high PCI score, poor ECOG performance
354 status, high CC score, longer surgery duration, and postoperative
355 complications were related to poor QoL, and that these factors were associated
356 with the severity of disease, complicated surgery, and prolonged recovery [2, 6,
357 7, 22, 23]. However, we found that PCI score, CC score, surgical duration,
358 hospitalization duration, and postoperative complications were not associated
359 with QoL in the perioperative period after HIPEC/CRS. This may be due to the
360 strict clinical criteria used in this study (e.g., 94.8% had an ECOG score ≤ 1 and
361 a median PCI score of 5.5 with some receiving adjuvant HIPEC who did not
362 have PSM) to enroll the patients with CRS/HIPEC, and this may have
363 contributed to a better baseline physical condition.
364 This study identified younger age (<55 years old) as a risk factor for poorer
365 perioperative decline in QoL and similar results have been reported by
366 previous studies [24, 25] Younger patients may have greater socioeconomic stress,

lower incomes, and weak family supports, and these would contribute to the feeling of hopelessness and these may result in a low QoL [25]. Our preliminary finding was younger age <55 years have poorer emotional functioning at early post-operative visit (S2). Although, further analyses are needed to include these factors in the prediction models and assess their roles in influencing QoL.

There are several strengths to this study. First, all of the patients were enrolled after the consensus of the MDT committee, and CRS/HIPEC was performed by experienced team members. Thus, the quality of perioperative care was consistent and well documented. Second, the associated clinical data were prospectively collected. In addition, to make sure that the patients could understand the questions, the questionnaires were performed by a single well-trained case manager in face-to-face interviews with the patients, and this could minimize detection bias and missing data. Third, this study focused on measuring the change in QoL in the perioperative period after CRS/HIPEC, and this could minimize interference from the subsequent adjuvant therapy.

The major limitation was some patients transferred back to their original hospital for subsequent treatment when their condition after CRS/HIPEC had become stable, so it was difficult to collect longer term questionnaires. A minor limitation was that this study included patients with different types of cancer

and cancer surgery. Moreover, subgroup analysis for patients with different treatment intend and preoperative status were not performed due to small sample size.

The balance of treatment and QoL is often a controversial issue. Our findings showed that although CRS/HIPEC resulted in a short-term decline in the QoL of patients, most functions and the severity of symptoms returned to the baseline level within 3 months after surgery. Understanding the clinical course may relieve the patients' anxiety over their disease. We also found that perioperative symptom severity and symptom interference with daily life in the MDASI-T were significantly correlated with the decline in specific functions. Therefore, it is important to continuously evaluate and provide timely care to improve the symptoms and symptom interference of patients undergoing CRC/HIPEC, and ultimately to improve their QoL.

CONCLUSION

Our findings of younger age and poor preoperative ECOG performance status may help MDT members to identify patients undergoing CRC/HIPEC who are at high risk of perioperative symptom distress and decline in QoL. Patient counseling and peri-operative support may be provided accordingly. QoL and

symptom severity convalescing after three months reiterate the importance of the MDT approaches towards an effective teamwork for CRS/HIPEC care.

ARTICLE HIGHLIGHTS

Research background

Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (CRS/HIPEC) for peritoneal surface malignancy can effectively control the disease, however it is also associated with adverse effects which may affect quality of life (QoL).

Research motivation

Investigations of perioperative QoL and symptom severity after CRS/HIPEC are limited. the impact on QoL of this treatment has also gradually become more important due to socio-economic considerations.

Research objectives

The main objective of this study was to investigate early perioperative QoL after CRS/HIPEC, which has not been discussed in Taiwan.

Research methods

We performed an observational, prospective, single-center cohort study and enrolled patients who received CRS/HIPEC in Chang-Gung Memorial Hospital in Chiayi between September 1, 2018 and February 28, 2021. We assessed QoL using the Taiwanese version of the MD Anderson Symptom Inventory (MDASI-T) and European Organization Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30). Participants completed the questionnaires before CRS/HIPEC (S1), at the first outpatient follow-up (S2), and 3 months after CRS/HIPEC (S3).

Research results

Most patients had a significant decline in physical and role function scores at S2, but that they returned to the preoperative status at S3. The most serious symptoms after surgery were fatigue and pain, and that pain returned to the preoperative status 3 months after surgery. There was no significant decline in global health status after surgery. Both items in the MDASI-T were significantly negatively correlated with the EORTC QLQ-C30 results. The important predictors of determinants of QoL were age ≥55 years old in emotional functioning at S2 ($\beta = -0.40$, $p < 0.05$), and performance status in preoperative

physical functioning (β = 21.49, p < 0.05) and role functioning at S3 (β=29.63, p<0.05).

Research conclusions

QoL and symptom severity improved or returned to baseline in most categories within 3 months after CRS/HIPEC. Understanding the clinical course may relieve the patients' anxiety over their disease. Our findings may help physicians with preoperative consultation and perioperative care.

Research perspectives

As this study was a relative small sample sized prospective study, larger studies with multiple centers and less influences factors are warranted to explore the QoL after HIPEC.

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Footnotes

Institutional review board statement: The study was reviewed and approved for publication by the Institutional Review Board of Chang Gung Medical Hospital (No. 201800726B0)

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

Figure legends

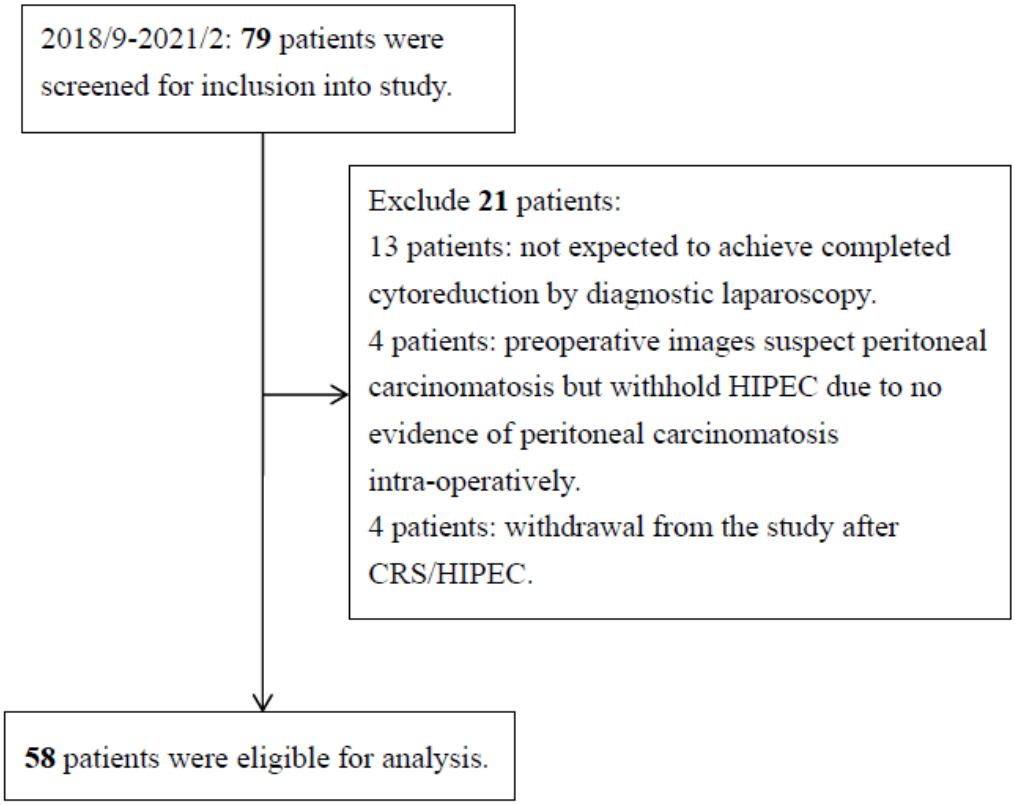

Figure 1. Flowchart of patient enrollment. CRS: cytoreductive surgery; HIPEC: hyperthermic intraperitoneal chemotherapy.

Table 1. Patients' characteristics and HIPEC parameters (n=58)

Variable	Number	Percentage
Sex		
Male	19	32.8
Female	39	67.2
Age at CRS+HIPEC, years (median, range)	60 (22-78)	
BMI, kg/m^2 (mean, SD)	24.3 (4.5)	
ECOG		
0-1	55	94.8
2	3	5.2
Comorbidity		
Hypertension	17	29.3
Diabetes mellitus	11	19.0
Hepatitis B	5	8.6
Hepatitis C	6	10.3
Primary or recurrent tumor		
Primary	41	70.7
Recurrent	17	29.3
Primary cancer		
Colorectal	9	15.5
Ovarian	15	25.9
Gastric	27	46.6
Others	7	12.1
Previous definitive surgery		
No	35	60.3
Yes	23	39.7
Previous systemic chemotherapy		
Never	22	37.9
1st line	23	39.7
2nd lines or more	13	22.4
PCI (median, range)	5.5 (0-39)	
Completeness of cytoreduction score		
0	46	79.3
1	8	13.8
2	1	1.7
3	3	5.2
Duration of peritonectomy, mins (median, range)	240 (0-610)	
Length of hospital stay, days (median, range)	13 (7-39)	
Surgical method		
Laparotomy	53	91.4
Laparoscopy	5	8.6
HIPEC regimen		
Cisplatin	43	74.1
Non-cisplatin	15	25.9
HIPEC indication		
Adjuvant	16	27.6
Curative	39	67.2

Palliation	3	5.2
Duration of HIPEC, mins		
60	46	75.9
90	12	20.7
Post-op complications		
No	6	10.3
Yes	52	89.7
Post-op complications		
Grade I	42	72.4
Grade II	6	10.3
Grade III	3	5.2
Grade IV	1	1.7
Nutrition (PGSGA score)		
A	42	85.7
B	7	14.3

Abbreviations: BMI, body mass index; ECOG, Eastern Cooperative Oncology Group performance status; PCI, peritoneal carcinomatosis index; PGSGA, Patient-Generated Subjective Global Assessment.

Table 2. Descriptive data of the EORTC QLQ-C30 and MDASI-T questionnaires (n=58)

Scales	Items	S1 (N=58)	S2 (N= 58)	S3 (N=55)	*P*-value*	The pairwise comparison between S1/S2 (*P*-value*)	The pairwise comparison between S2/S3 (*P*-value*)	The pairwise comparison between S1/S3 (*P*-value*)
QLQ-C30	30	53.5 (8.6)	57.3 (9.8)	54.0 (9.8)	0.066	0.080	0.152	0.960
Global health status	2	60.3 (19.4)	56.6 (15.4)	64.4 (17.5)	0.065	0.486	0.051	0.439
Functional scales	15							
Physical functioning	5	82.2 (15.0)	70.5 (19.0)	80.6 (18.2)	**0.001**	**0.001**	**0.007**	0.881
Role functioning	2	78.7 (23.9)	64.1 (23.9)	76.4 (25.2)	**0.003**	**0.004**	**0.022**	0.863
Emotional functioning	4	74.6 (14.8)	78.3 (17.2)	80.6 (17.8)	0.152	0.449	0.743	0.134
Cognitive functioning	2	84.8 (17.2)	85.3 (13.3)	87.3 (18.4)	0.700	0.981	0.807	0.697
Social functioning	2	76.4 (25.8)	74.7 (22.8)	82.7 (20.0)	0.155	0.914	0.157	0.317
Symptom scales	13							
Fatigue	3	26.2 (16.5)	37.5 (21.7)	32.1 (16.9)	**0.005**	**0.004**	0.269	0.215
Pain	2	14.9 (18.4)	27.0 (19.5)	14.2 (17.7)	**<0.001**	**0.002**	**0.001**	0.978
Nausea and vomiting	2	9.8 (21.2)	8.0 (16.0)	12.7 (19.0)	0.413	0.875	0.386	0.682
Dyspnea	1	12.1 (17.3)	17.8 (20.0)	9.7 (15.3)	**0.044**	0.189	**0.041**	0.756
Insomnia	1	23.6 (27.2)	24.1 (26.3)	21.2 (22.6)	0.813	0.992	0.815	0.876
Appetite loss	1	21.3 (23.9)	27.6 (28.0)	27.3 (22.3)	0.311	0.361	0.998	0.408
Constipation	1	12.1 (23.9)	12.1 (20.4)	17.6 (25.5)	0.357	1.000	0.424	0.424
Diarrhea	1	12.6 (19.6)	11.5 (19.3)	17.0 (21.2)	0.314	0.949	0.316	0.485
Financial difficulties	1	21.3 (24.7)	21.3 (26.3)	17.0 (23.0)	0.571	1.000	0.627	0.627
MDASI-T	19							
Symptom severity	13	14.8 (12.5)	16.8 (12.8)	15.3 (15.2)	0.726	0.722	0.836	0.980
Degree of interference with life	6	9.6 (9.5)	10.7 (10.0)	7.5 (8.6)	0.186	0.791	0.166	0.468

Abbreviations: MDASI-T, MD Anderson Symptom Inventory - Traditional version; QLQ-C30, Quality of Life-Core 30-item.

S1, the first visit before CRS/HIPEC; S2, the second visit at the first outpatient follow-up after CRS/HIPEC; S3, the third visit at the outpatient visit 3 months after CRS/HIPEC

The data are presented as the mean and standard deviation of the scores (in parentheses)

*P-values were calculated using one-way analysis of variance (ANOVA). **Bold**: $p < 0.05$

Table 3. Relationships between the EORTC QLQ-C30 and its related factors at three time periods (S1, S2, and S3)

	Global health status			Physical functioning			Role functioning			Emotional functioning			Cognitive functioning			Social functioning		
Characteristic	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3
Age	-0.55	-0.96	-0.01	-0.61	-2.29*	-1.01	-0.79	-0.83	-2.26*	-0.49	1.08	-0.81	-0.7	-0.5	-1.11	-1.21	-2.07*	-1.99
Sex	-0.67	0.14	-1.11	-0.03	-0.18	-0.07	-1.33	-0.01	-1.43	0.31	0.33	-0.15	-0.44	0.6	-0.07	-0.56	-0.24	-0.69
ECOG	1.21	-0.84	0.33	2.78**	0.56	2.07*	3.87***	-1.02	1.49	1.29	0.05	0.01	1.92	1.79	-0.69	-0.47	-1.56	-1.04
HTN	-1.23	-0.7	-0.44	-0.56	-0.84	-0.29	-1.47	-0.16	-0.05	-0.3	0.52	-0.11	0.41	-1.07	-0.4	-1.32	-1.23	-0.32
DM	-0.05	-0.41	-2.03	-0.06	-0.32	-2.07	-0.7	0.48	-0.97	-0.48	0.7	-1.2	0.96	0.55	-0.83	-0.77	-1.41	-1.58
HBV	0.24	0.24	1.03	1.39	0.96	0.76	-0.12	0.40	-0.03	-0.07	1.13	0.08	0.19	1.55	0.5	-2.71*	-0.54	-0.07
HCV	1.2	0.18	-0.75	0.95	0.36	0.08	-0.49	0.32	0.28	0.17	1.34	0.96	-0.62	-0.15	0.92	-0.41	0.59	-0.07
Primary or recurrent tumor	-0.98	-0.39	-1.04	-2.03	-0.54	-0.82	-1.78	-0.73	-1.32	-0.79	0.94	0.24	-0.15	1.48	0.74	-1.52	0.58	-0.39
Primary cancer[a]	1.36	1.43	1.36	0.48	0.46	0.48	0.43	0.60	0.43	0.63	0.36	0.63	1.12	0.59	1.12	1.00	0.93	1
Previous definitive surgery	-1.33	-0.83	-1.16	-1.25	-1.12	-1.14	-0.81	-0.66	-0.51	-0.63	0.92	0.27	-0.78	-0.07	-0.26	-1.31	0.24	-0.4
Previous systemic chemotherapy	-1.57	-1.86	-2.15*	-0.99	-0.9	-1.1	-1.37	-1.05	-1.52	-0.89	0.43	-0.93	0.29	0.45	-1	-1.37	-0.71	-1.99
PCI[b]	-0.05	-0.02	0.10	-0.15	-0.12	-0.13	-0.15	-0.12	-0.05	-0.22	-0.04	0.04	-0.11	0.03	-0.01	-0.01	-0.05	-0.05
CC[a]	0.93	1.14	0.48	1.03	1.07	0.37	0.53	1.07	0.29	1.45	0.06	0.35	0.38	0.53	0.3	0.72	0.85	0.13
Duration of peritonectomy (min)[b]	-0.06	-0.18	0.11	0.18	-0.21	0.05	0.09	-0.37	-0.01	0.01	0.04	0.09	-0.14	0.04	-0.03	-0.09	-0.04	0.05
LOS (days)[b]	-0.13	0.14	-0.03	-0.02	0.10	-0.07	0.00	0.06	-0.12	-0.01	0.20	0.03	-0.26	0.13	-0.05	0.09	0.18	0.07
Surgical method	0.64	-0.01	0.47	0.54	0.3	0.65	1.18	0.72	0.11	2.11*	1.6	1.14	0.65	2.87**	1.4	2.87**	0.72	-0.22
HIPEC regimen	-1.11	-0.63	-0.52	-0.39	0.89	2.56*	-0.15	0.07	-0.12	-0.04	-0.35	0.63	-0.66	0.44	1.93	-0.54	-1.38	0.39
HIPEC indication[a]	0.95	0.15	1.16	1.34	0.44	0	0.39	0.47	0.01	0.93	0.11	0.15	0.02	0.22	0.08	1.54	1.39	0.15

Duration of HIPEC (mins)	0.82	0.44	0.37	1.01	-0.7	-2.13*	0.6	0.48	0.42	0.62	1.28	-0.04	0.01	-1.46	-2.43*	0.84	1.38	-0.1
Post-op complications[a]	0.62	0.54	2.05	0.69	0.88	0.19	0.51	0.99	0.67	0.4	0.34	1.34	2.24	1.51	1.25	0.48	1.15	2.61
PGSGA	1.84	0.49	1.08	0.79	0.14	1.28	-1.27	-0.78	0.9	1.16	-0.19	-0.44	1.25	0.42	1.2	-0.55	0.74	0.6
MDASI-T																		
SS[b]	-0.48***	-0.34	-0.70	-0.38	-0.46	-0.52	-0.30	-0.45***	-0.48***	-0.34**	-0.49***	-0.64***	-0.54***	-0.20	-0.72***	-0.24	-0.33*	-0.61***
DIL[b]	-0.54***	-0.49***	-0.69***	-0.43***	-0.63***	-0.66	-0.47***	-0.60***	-0.69***	-0.43***	-0.43***	-0.72***	-0.39**	-0.28*	-0.67***	-0.53***	-0.52***	-0.78***

Abbreviations: BMI, body mass index; CC, completeness of cytoreduction; DIL, degree of interference with life; DM, diabetes mellitus; ECOG, Eastern Cooperative Oncology Group performance status; *HBV*, hepatitis B; *HCV,* hepatitis C; HTN, hypertension; PCI, peritoneal carcinomatosis index; PGSGA, Patient-Generated Subjective Global Assessment; SS, symptom severity; LOS, length of hospital stay; MDASI-T, MD Anderson Symptom Inventory-Taiwan version.

[#] S1, the first visit before CRS/HIPEC; S2, the second visit, the first outpatient follow-up visit after CRS/HIPEC; S3, the third visit, the outpatient visit 3 months after CRS/HIPEC

[a] F coefficients; [b] r coefficients; *p < 0.05, **p < 0.01, ***p < 0.001

Table 4: Multiple regression analysis of QoL at the three time periods (S1, S2, and S3).

	Global health status			Physical functioning			Role functioning			Emotional functioning			Cognitive functioning			Social functioning		
Characteristic	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3	S1	S2	S3
Age[a]	-0.04	-0.09	-0.20	0.12	0.12	0.05	0.44	-0.11	0.36	-0.06	-0.40*	-0.06	-0.22	0.10	-0.04	0.15	0.33	0.23
Sex[a]	-3.42	3.04	-0.90	-1.51	0.03	-0.02	-8.47	4.16	-7.64	2.26	3.28	2.86	-3.84	2.48	3.10	1.91	3.41	-0.02
ECOG[a]	11.48	-3.84	6.95	21.49*	8.54	15.71	14.12	-15.01	29.63*	4.44	-6.42	-7.51	12.7636	6.65	-16.70	-15.26	-17.76	-13.80
HBV[a]	1.14	-2.14	-7.53	-7.03	-11.47	-9.52	-2.91	-9.50	-2.33	0.34	-8.79	-5.72	5.04	-11.76	-12.04	4.86	-2.02	-8.07
Previous systemic chemotherapy[a]	7.88	4.22	5.17	5.12	0.63	-0.89	9.32	-0.47	2.49	3.04	-6.04	-5.53	-0.57	-2.98	-3.83	6.84	-1.42	-0.12
Surgical method[a]	-4.57	-0.44	0.86	-2.74	0.36	8.32	7.11	8.92	-4.39	9.93	10.61	11.54	-7.77	17.23**	16.78*	33.22**	16.73	2.54
HIPEC regimen[a]	0.65	1.41	6.69	-0.93	-7.51	-6.67	-3.94	-4.08	4.79	-2.55	-0.21	-0.23	-0.85	-2.09	-5.98	-1.76	6.71	-0.76
MDASI-T																		
SS[a]	-0.45*	-0.07	-0.54**	-0.21	-0.15	-0.01	-0.17	-0.15	0.18	-0.10	-0.41	-0.11	-0.68**	0.07	-0.52*	0.23	0.06	0.10
DIL[a]	-0.75*	-0.71*	-0.64	-0.44	-1.08*	-1.37**	-0.78	-1.39***	-2.11***	-0.61*	-0.65*	-1.49***	-0.32	-0.46*	-0.78*	-1.48***	-1.04**	-1.89***
Adjusted R^2	0.40	0.28	0.63	0.35	0.47	0.55	0.32	0.41	0.58	0.27	0.40	0.58	0.37	0.32	0.64	0.45	0.37	0.65

Abbreviations: DIL, degree of interference with life; ECOG, Eastern Cooperative Oncology Group performance status; *HBV*, hepatitis B; SS, symptom severity; MDASI-T, MD Anderson Symptom Inventory-Taiwan version.

[#] S1, the first visit before CRS/HIPEC; S2, the second visit, the first outpatient follow-up visit after CRS/HIPEC; S3, the third visit, the outpatient visit 3 months after CRS/HIPEC

[a] β coefficients; *p < 0.05, **p < 0.01, ***p < 0.001