

ORIGINAL ARTICLE

Quality of life after cytoreductive surgery and HIPEC: A single centre prospective study

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Summary

Purpose: Cytoreductive surgery (CRS) plus hyperthermic intraperitoneal chemotherapy (HIPEC) has become a crucial method in the management of peritoneal metastasis. This study evaluated the Quality of Life (QoL) post CRS plus HIPEC.

Methods: 80/95 patients underwent CRS plus HIPEC at the Metaxa Cancer Hospital, Piraeus, Greece from 06/2011 to 06/2015 and completed the colorectal version of the Functional Assessment of Cancer Therapy questionnaire (FACT-C, version 4) at 1 week pre-operatively and at 1, 3, 6, 12, 18, 24 months post-operatively. The subscales assessed were the physical, social/family, emotional and functional well-being.

Results: In all subscales, fluctuations in the scores indicated a worsening of QoL in the first 3 post-operative months, followed by improvement back to pre-operative levels and even better scores later on. Statistical improvement was proven for the physical and emotional well-being subscales.

Conclusions: The significant improvement in the physical well-being is attributed to the eradication of symptoms, whereas the relevant improvements in the emotional well-being subscale are explained both by the pre-operative desperation of the diagnosis or relapse of malignancy, and the post-operative hopefulness after a successful operation.

Key words: cytoreductive surgery, emotional well-being, FACT-C, HIPEC, physical well-being, quality of life

Introduction

CRS plus HIPEC has proven to be a crucial method in the cure, treatment and management of peritoneal surface malignancy (PSM), with acceptable results in terms of symptom relief and life-prolonging [1,2]. Being a major and extensive procedure, CRS plus HIPEC requires careful and appropriate patient selection in order to maximize the intended benefits [3].

The origin of cancer, the peritoneal cancer index (PCI, indicating the extent of the disease), the completeness of cytoreduction score (CC, indicating the

remaining disease) and the presence of comorbidities are some of the factors that have been identified to have an impact on morbidity, mortality, survival and, possibly, QoL. Nevertheless, up to now, a small number of studies has been performed on the QoL outcomes post-CRS plus HIPEC procedures [4,5].

The purpose of our study was to evaluate the QoL post-CRS plus HIPEC and the fluctuations that can be observed in different post-operative periods, but also to attempting an initial description and correlation with influential factors.

Methods

From June 2011 to June 2015, 95 patients underwent CRS plus HIPEC at the Metaxa Cancer Hospital, Piraeus, Greece.

Primary cancer sites can be observed in Table 1. Mean age was 54.8 years (range 29-80) and female patients were more than male (58 and 37, respectively).

Intra-operative staging of the peritoneal metastasis was achieved with the use of PCI, whereas residual disease was assessed with the use of CC score.

Cytoreductive procedures, including peritonectomies and visceral resections, were performed according to the technique described by Sugarbaker and HIPEC was performed with the closed abdomen technique [6].

The chemotherapeutic agents that were utilized for each cancer origin is shown in Table 2, and were chosen according to previously described protocols [7].

Eighty out of 95 patients (84.2%) consented to participate in our research by allowing us to utilize their demographic data and by completing the FACT-C, version 4, questionnaire (Functional Assessment of Cancer Therapy-Colorectal) [8,9], and were included in our analysis only if they had completed at least the pre-operative and the first post-operative questionnaire.

The FACT-C (v4) questionnaire was offered at the patients 1 week pre-operatively, and at their regular

follow-up appointments at 1, 3, 6, 12, 18 and 24 months post-operatively.

At this point, we deemed necessary to analyze in more depth the 5 subscales of the questionnaire, in order to facilitate a better understanding of our findings.

The 5 subscales are physical well-being (PWB), social/family well-being (SWB), emotional well-being (EWB), functional well-being (FWB) and supplement anxious situations (SAS).

PWB, SWB and FWB subscales consist of 7 questions, with possible answers giving 0-4 points, and therefore leading to possible scores from 0 to 28, whereas EWB consists of 6 questions, and subsequent possible overall scores of 0-24. The SAS subscale differs, since it consists of 7 initial questions (0-4 points for each) and an extra two questions (again 0-4 points), depending on the presence of a stoma or not, therefore leading to possible scores from 0 to 28 or 0 to 36.

When interpreting the relevant results, a researcher must bear in mind that for SWB and FWB, higher values indicate a better QoL, but the opposite stands for PWB and EWB (higher scores indicate worse QoL). SAS consists of questions where for some of them a higher score (0-4) indicates better QoL and for others higher scores indicates a worse QoL, therefore a simple analysis and interpretation based solely on the total score, would be of no benefit.

Apart from recording the trends and changes in our patients' QoL, we also attempted to correlate them to a number of parameters, such as the origin of cancer, the PCI, the CC score, the age and sex, the chemotherapeutic agent that was administered during HIPEC and the development of late complications (resulting in further hospitalization).

Statistics

SPSS 23.0 statistical package was used for statistical analyses which were carried out by utilizing paired Student's t-test and calculating the non-parametric correlation coefficient p value, where values <0.05 were considered statistically significant.

Table 1. Primary cancer sites and number of patients

Primary site	Patients, n
Ovary	28
Colon	17
Pseudomyxoma peritonei	15
Mesothelioma	7
Stomach	5
Endometrium	4
Rectum	2
Sarcoma	2

Table 2. Chemotherapeutic agents

Tumor type	Agents and dosages	Time and temperature
Ovarian cancer	Sensitive: Cisplatin 100mg/m ² Paclitaxel 175mg/m ²	60 min/42,5°C
	Resistant: Doxorubicin 35mg/m ² Paclitaxel 175mg/m ²	
Mesothelioma	Cisplatin 50mg/m ² Doxorubicin 50mg/m ²	60 min/42,5°C
Pseudomyxoma	Mitomycin 15mg/m ²	60 min/42,5°C
Gastric cancer	Cisplatin 50mg/m ² Doxorubicin 50mg/m ²	90 min/42,5°C
Colon cancer	Oxaliplatin 150mg/m ² Irinotecan 200mg/m ²	60 min/42,5°C

Results

All scores in every subscale and Figures with the trends at all selected time points can be observed in Table 3 and Figure 1, respectively. A more extensive analysis of each subscale findings follows:

Physical well-being (PWB) scores increased sharply in the first post-operative month (indicating a worse QoL, compared to pre-operatively QoL), but decreased steadily over the first year, reaching the pre-operative values. These changes were statistically significant ($p < 0.02$).

Social/Family well-being (SWB) scores decreased during the first 3 post-operative months (worsening of QoL), increased back to pre-operative values at 6 months, and this pattern continued at 12 months and so on, but without significant change.

Emotional well-being (EWB) scores tended to increase immediately post-operatively (worsening of QoL), but reached the pre-operative levels at 3 months, and then showed a continuous, statistically significant ($p < 0.001$) decrease.

Functional well-being (FWB) scores showed a steady decrease over the first 3 post-operative

months (worsening of QoL), but started to increase at 6 months, reaching pre-operative levels at 12 months. Nevertheless, no statistical significance was noted.

Further analysis identified factors that contributed to either worsening or improvement of QoL, as this could be expressed through the questionnaires ($p < 0.05$). More specifically:

1. Younger age was related with improvement of QoL.
2. Female gender was related with worsening of QoL.
3. Lower PCI scores were related with improvement of QoL.
4. Better CC scores were related with improvement of QoL.
5. As far as chemotherapeutic agents are concerned, mitomycin was related with improvement of QoL and oxaliplatin with worsening of QoL.
6. The presence of a stoma was related with worsening of QoL.
7. The absence of relatives and a supportive environment was related with worsening of QoL.

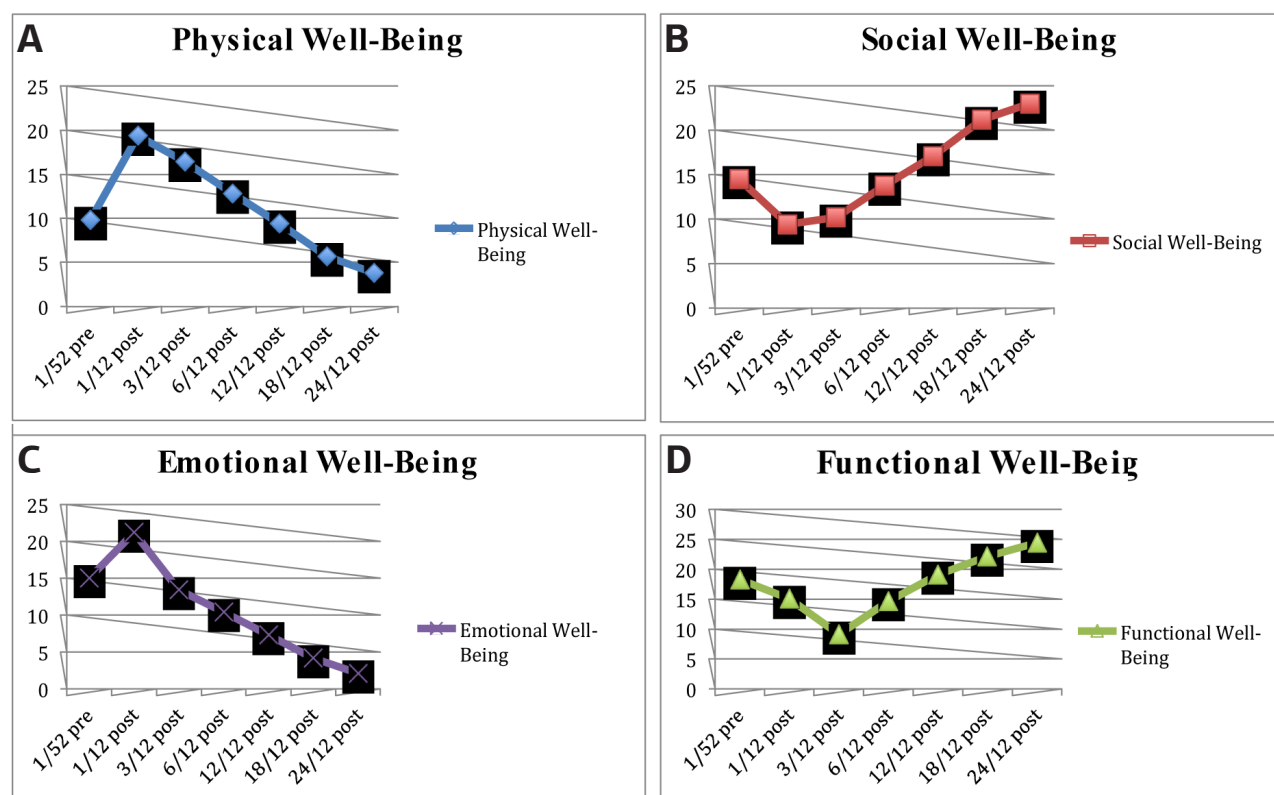


Figure 1. A: Physical well-being: After an initial postoperative worsening in physical well-being, improvement above the pre-operative levels was found after 12 months ($p < 0.02$). **B:** Social well-being: Despite an improvement in social well-being 1 year postoperatively, no statistical significance was found. **C:** Emotional well-being: A statistically significant improvement ($p < 0.001$) in emotional well-being is demonstrated after the 3rd postoperative month. **D:** Functional well-being: Functional well-being reached the preoperative levels at 12 months postoperatively, and continued to improve, without, though, being statistically significant.

Table 3. FACT-C subscale mean scores and SD at various timepoints

	1 week pre-op (n=80) n (%)	1 month post-op (n=80) n (%)	3 months post-op (n=78) n (%)	6 months post-op (n=73) n (%)	12 months post-op (n=69) n (%)	18 months post-op (n=58) n (%)	24 months post-op (n=40) n (%)
PWB	9.8 (10.5)	19.4 (4.8)	16.4 (5.3)	12.8 (9.1)	9.4 (10.1)	5.7 (9.8)	3.8 (6.2)
SWB	14.5 (4.1)	9.4 (7.1)	10.2 (3.2)	13.8 (3.6)	17.1 (4.9)	21.2 (5.1)	23 (5.3)
EWB	15 (4.8)	21.2 (2.4)	13.4 (2.1)	10.4 (1.8)	7.3 (1.3)	4.2 (1.1)	2.1 (0.8)
FWB	18.3 (12.1)	15.1 (4.3)	9.1 (3.1)	14.7 (3.9)	19.1 (5.1)	22.1 (5.6)	24.4 (5.8)

For abbreviations see text

Discussion

Patients with gastrointestinal or gynecological malignancies that result in peritoneal metastases have been proven to have dismal survival, with significant morbidity and mortality, mainly due to high disease burden within the abdominal cavity [10].

Complete cytoreductive surgery (CC₀/CC₁) plus HIPEC may prolong survival in appropriate candidates.

Not many studies have been performed with a prospective design, with evaluation of patient pre and post CRS plus HIPEC status. Certain limitations, such as a small sample and specified tumor sites, have to be taken into consideration [11].

However, a number of researchers from specialized centres have recently focused on QoL after such procedures, by using a variety of tools, and came to a common conclusion: a worsening of QoL must be expected the first 3 to 6 post-operative months, but then QoL improves back to pre-operative levels, and, in some cases, even higher than those [12-15].

In our study, we chose to utilize the Functional Assessment of Cancer Therapy Questionnaire, and specifically the colorectal version, as we considered that this would assess more accurately the consequences and perceptions after CRS plus HIPEC, taking a number of relevant factors into account (bowel resections, stoma creations and gastrointestinal complications related to bowel habits, diet etc).

Before interpreting the results, it is of great significance to mention that our sample decreased over the 2-year follow-up period down to 50%. This is due to the high mortality rates that accompany CRS and HIPEC procedure.

Moreover, it should be taken into account that patients who would demonstrate a worsening in their QoL, would be those suffering from complications and probable relapses, who eventually passed away at some point, and this could be considered as a limitation in our study.

Our results came to confirm those of previous studies with regards to the trends in QoL but also shed some light in particular aspects, as expressed by the subscales of the FACT-C questionnaire.

The *physical well-being scale* score demonstrates a post-operative sharp increase (worse QoL), that can be attributed to factors like pain, nausea, exhaustion and spending time in bed, which are expected after such extensive procedures with significant post-operative morbidity. Progressively, scores decrease (improvement of QoL), and that was proven as statistically significant.

The *social/family well-being scale* follows a similar trend, with immediate post-operative worsening of QoL and subsequent improvement, but these changes do not appear to be statistically significant. In an attempt to interpret that, we are inclined to believe that the procedure on its own, does not change the attitude and behavior of friends and family members towards the patient. This is particularly unpleasant, as pre-operative scores were already indicative of unsatisfactory social and family QoL, and that is unfortunately related to a more generalized approach and perception of the society with regards to patients being treated for cancer.

The *emotional well-being scale* is of great interest, in terms of interpretation. First of all, the pre-operative score is indicating a significantly poor QoL. This can be explained as patients have recently found out about their diagnosis or a disease relapse (being sad and nervous) and as they are uncertain and anxious about the outcome of the operation (and consequently afraid of dying). This gets even worse post-operatively, due to prolonged in-hospital stays, complications, coping with new stomas, anxiety about post-operative tests and imaging etc. Nevertheless, as time goes by and patients get more used to their new status and doing better, their emotional health improves too, and this turns out to be a statistically significant change. Similar estimates have been discussed in previous studies [16].

At this point, it is worth mentioning that the number of patients who would have a worsening (overall and emotional) QoL due to further relapses or complications, was deceased at the intervals between the assessment time points.

The *functional well-being scale* differs from the rest of the subscales, as it still indicates a worsening QoL at 3 months post-operatively (when the rest subscales indicate improving QoL), but then follows the expected trend of improvement to pre-operative levels. This subscale examines factors as enjoying life and going back to work, which are expected to recover more slowly, but still, the changes were not statistically significant.

As far as the specific factors that were proven to influence the changes in QoL are concerned, our experience led to some simple explanations:

Younger age of the patient equals less comorbidities, possibly a diagnosis of disease at earlier stages, and potentially a larger supportive group of friends and family. Lower PCI scores demonstrate a lower initial extent of peritoneal disease, which can indicate a less aggressive cancer type and a higher chance of achievement of a better CC score, and better CC scores, therefore minimal or none at all residual disease, predispose to less complications, lower chance of relapse and consequently better QoL. The connections made between specific chemotherapeutic agents and QoL may be attributable to each agent's side effects and cytotoxicity, whereas the presence of a stoma relates to a worse QoL, through inability to care for the stoma, being embarrassed by it, and partner's and family's approach towards it.

In the context of a possibly limited life expectancy, physical and emotional health improvements appear to be of great importance, and should definitely be advertised during the pre-operative decision making.

Lastly, we need to discuss the importance of a supportive environment around these patients. Unfortunately, in Greece, and specifically during times when the most harsh consequences of the financial crisis fall on the health system and particularly on patients with limited life expectancy, this supportive environment is not sufficiently developed.

We are inclined to believe that if our patients and their families have had specialized teams of nurses, psychologists etc to prepare them prior to surgery and working with them on the impact on their QoL of potential complications, QoL would not decline that much post-operatively and would have chances of reaching even higher levels later on.

Conclusions

On the whole, we can conclude that in carefully selected groups of patients, the aspects of QoL that benefit the most after a CRS plus HIPEC procedure, are those of physical and emotional well-being, as patients have no more physical signs and complications of their illness and as they have more hope and less anxiety, respectively. On the other hand, the same cannot be assumed for social well-being because these factors were already heavily influenced pre-operatively, as the procedure does not change the society's understanding and behavior towards cancer patients.

Taking into account the unique characteristics of CRS and HIPEC, we plan to design a more focused QoL questionnaire, that will provide more comprehensive information related to this specific type of procedures.

Conflict of interests

The authors declare no conflict of interests.

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