

Peer Review File

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Reviewer comments:

Comment 1: Patients in this study were evaluated two weeks after surgery, allowing relative improvement to be observed at a time point of three months. In a cross-sectional study, Ford et al. Also concluded that an acceptable quality of life can be achieved within three months. However, most studies have found that it takes 6-12 months for patients to return to baseline quality of life. What are the potential reasons for the inconsistent results?

Reply 1: We thank the reviewer for raising this point and we agree that there are seemingly conflicting conclusions from several of the papers. While papers that examined QOL at both 2 weeks and 3 months noted some improvement between these two timepoints, papers that first measured QOL at 3 months found a negative trend at this timepoint. QOL at 3 months typically remained below baseline in all studies, however. Some of the heterogeneity in results is likely due to the wide range of sample sizes, but the 6-12 month period was most consistently identified as the period in which patients returned to baseline. With regard to the paper by Ford et al, this study sought to determine whether patients achieved “acceptable” QOL despite not measuring pre-operative baseline QOL. Whether this level of “acceptable” QOL is equal to the baseline QOL of patients in that study is difficult to say and limits our ability to compare this paper to prospective studies. To clarify this, we have added a line to the section on “Global Quality of Life” on Page 5 to clarify that Ford et al do not measure baseline QOL.

Comment 2: In most studies, the overall quality of life decreased dramatically after surgery and eventually returned to baseline level at about 6-12 months. This improvement seems to be sustained among the long-term survivors. How to improve the overall quality of life after surgery?

Reply 2: Thank you to the reviewer for this question. We agree that our submitted manuscript did not expand on the types of interventions that improve patients’ post-operative quality of life. We have identified multiple sources that describe evidence-based interventions to improve post-operative QOL, and as such we have added the following text following our reference to survivorship programs in the Conclusions and Future Directions section on Page 10:

To maintain improvements in QOL, these programs should focus on interventions that have been shown to improve QOL in post-operative cancer patients. Patient education, psychological counseling, exercise programs, and cognitive therapy have all been shown to be effective in improving post-operative QOL in various cancer populations.

Comment 3: The lack of public data on the immediate quality of life after surgery may limit the ability of doctors to design programs to treat and prevent common problems. In order to better

solve the postoperative symptoms of patients, this critical period needs further attention. What are the potential reasons for the lack of public data on immediate postoperative quality of life, and how to pay more attention to this critical period in future research?

Reply 3: We thank the reviewer for this question, and we concur that the lack of data in the immediate post-operative period limits our ability to improve QOL in this period. Unfortunately, we are not aware of any strong evidence as to why this type of data is lacking. It would seem likely to us that the number and frequency of post-operative surveys are limited in order to decrease survey fatigue and improve patient response rate, however we cannot confirm this. In order to address this point without speculating, we have added the following text to the Conclusions and Future Directions section on Page 10:

It is not clear why there is a lack of data in the first three months after surgery, but to better address the symptoms that patients face following surgery, this critical period requires further attention.

Comment 4: The quality of emotional life is the least affected of all areas, and many studies have shown that the quality of emotional life after surgery is improved from baseline; however, the problem of long-term survivors is persistent depression. What are the treatments for persistent depression?

Reply 4: Thank you to the reviewer for this question. While all patients with depression may benefit from general interventions such as anti-depressants and counseling, there may be particular treatments that would be useful in cancer patient populations. For example, there is some evidence that “prehabilitation” programs focusing on pre-operative psychological counseling may improve depression rates in this population. To clarify this point, we have added the following text to the Conclusions and Future Directions section on Page 10:

Depression, a similarly prevalent symptom in post-operative patients, is often treated by a combination of anti-depressant therapy, neurostimulation, and psychiatric counseling.⁷⁰ Pre-operative psychiatric “prehabilitation” programs may also play an important role in decreasing rates of depression in future patients.

Comment 5: There are several subgroups of patients who have improved significantly. For example, patients with PMP secondary to low appendix mucinous tumors (lamns) have an average survival time of about 20 years after successful cell reduction. What are the common characteristics of these subgroups?

Reply 5: This point was not entirely clear in our manuscript and we thank the reviewer for bringing this to our attention. There is significant heterogeneity in the response to CRS/HIPEC in different pathologies, and it can be difficult to compare outcomes from different primary neoplasms. A useful comparison, however, may be different tumors arising from the same site. For example, patients treated with CRS/HIPEC for cancers of the appendix have varying outcomes

based on the histology of the primary tumor. Higher grade tumors and those with high-risk features on histology such as signet rings experience worse survival. To further explain this in our manuscript, we have added the following text to the Conclusions and Next Directions section on page 9:

Survival benefits are more limited in the treatment of more aggressive, high-grade neoplasms; despite also arising from the appendix, appendiceal adenocarcinoma has a median overall survival of 91 months, decreasing to only 32 months with the presence of high-risk signet ring cells.⁶⁷ Aggressive neoplasms from other sites in the abdomen have similar or shorter expected survival, but the overall trend in survival after CRS/HIPEC has been incremental improvement.

Comment 6: With regard to somatic symptoms, postoperative pain relief is generally observed, but other gastrointestinal and physical symptoms are still common. How to improve the physical symptoms of postoperative patients?

Reply 6: Thank you for this question. We agree that expanding on specific interventions would be useful for readers, and as such have added the following text to the Conclusions and Future Directions section on Page 10:

Some somatic symptoms such as fatigue and insomnia may be improved by [survivorship] programs, while others would likely benefit from pharmacologic interventions, Gastrointestinal symptoms are particularly prevalent and can be addressed with patient-tailored regimens of laxatives, pro-motility agents, and anti-diarrheal agents.