Original Article

Effect of Intestinal Resection on Quality of Life in Crohn’s Disease

Emily K. Wright, a Michael A. Kamm, a Peter De Cruz, a Amy L. Hamilton, a Kathryn J. Ritchie, a Efrosinia O. Krejany, a Alexandra Gorelik, b Danny Liew, b Lani Prideaux, a Ian C. Lawrance, c Jane M. Andrews, d Peter A. Bampton, e Miles P. Sparrow, f Timothy H. Florin, g Peter R. Gibson, h Henry Debinski, i Richard B. Gearry, j Finlay A. Macrae, k Rupert W. Leong, l Ian Kronborg, m Graeme Radford-Smith, n Warwick Selby, o Michael J. Johnston, a Rodney Woods, a P. Ross Elliott, a Sally J. Bell, a Steven J. Brown, a William R. Connell, a Paul V. Desmond a

aDepartment of Gastroenterology, St Vincent’s Hospital and University of Melbourne, Melbourne, VIC, Australia
bMelbourne EpiCentre, University of Melbourne and Melbourne Health, Melbourne, VIC, Australia
cCentre for Inflammatory Bowel Diseases, Fremantle Hospital and University of Western Australia, Fremantle, WA, Australia
dDepartment of Gastroenterology and Hepatology, Royal Adelaide Hospital and University of Adelaide, Adelaide, SA, Australia
eDepartment of Gastroenterology and Hepatology, Flinders Medical Centre and Flinders University, Adelaide, SA, Australia
fDepartment of Gastroenterology, Alfred Health and Monash University, Melbourne, VIC, Australia
gDepartment of Gastroenterology, Mater Health Services, University of Queensland, Brisbane, QLD, Australia
hDepartment of Gastroenterology, Alfred Health and Monash University, Melbourne, VIC, Australia
iMelbourne Gastrointestinal Investigation Unit, Cabrini Hospital, Melbourne, VIC, Australia
jDepartment of Medicine, University of Otago, Christchurch, New Zealand
kDepartment of Colorectal Medicine and Genetics, and Department of Medicine, Royal Melbourne Hospital and University of Melbourne, Melbourne, VIC, Australia
lGastroenterology and Liver Services, Concord and Bankstown Hospitals and University of New South Wales, Sydney, NSW, Australia
mDepartment of Gastroenterology and Western Hospital, Melbourne, VIC, Australia
nDepartment of Gastroenterology, Royal Brisbane and Womens Hospital, and IBD Group Queensland Institute of Medical Research, University of Queensland, Brisbane, QLD, Australia
oAW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Sydney, NSW, Australia

Corresponding author: Professor Michael Kamm, MD, PhD, St Vincent’s Hospital, Victoria Parade, Fitzroy 3065, Melbourne, VIC, Australia. Tel: + 61 3 9417 5064; Fax: + 61 3 9416 2485; Email: mkamm@unimelb.edu.au

Abstract

Introduction: Patients with Crohn’s disease have poorer health-related quality of life (HRQoL) than healthy individuals, even when in remission. Although HRQoL improves in patients who achieve drug-induced or surgically induced remission, the effects of surgery overall have not been well characterised.

Methods: In a randomised trial, patients undergoing intestinal resection of all macroscopically diseased bowel were treated with postoperative drug therapy to prevent disease recurrence. All patients were followed prospectively for 18 months. C-reactive protein (CRP), Crohn’s Disease Activity Index (CDAI), and faecal calprotectin (FC) were measured preoperatively and at 6, 12, and 18 months. HRQoL was assessed with a general [SF36] and disease-specific [IBDQ] questionnaires at the same time points.
Effect of Surgery on Quality of Life in Crohn’s

Results: A total of 174 patients were included. HRQoL was poor preoperatively but improved significantly ($p < 0.001$) at 6 months postoperatively. This improvement was sustained at 18 months. Females and smokers had a poorer HRQoL when compared with males and non-smokers, respectively. Persistent endoscopic remission, intensification of drug treatment at 6 months, and anti-tumour necrosis factor therapy were not associated with HRQoL outcomes different from those when these factors were not present. There was a significant inverse correlation between CDAI, [but not endoscopic recurrence, CRP, or FC] on HRQoL.

Conclusion: Intestinal resection of all macroscopic Crohn’s disease in patients treated with postoperative prophylactic drug therapy is associated with significant and sustained improvement in HRQoL irrespective of type of drug treatment or endoscopic recurrence. HRQoL is lower in female patients and smokers. A higher CDAI, but not direct measures of active disease or type of drug therapy, is associated with a lower HRQoL.

Keywords: Crohn’s disease; inflammatory bowel disease; postoperative; health-related quality of life; biologicals; smoking

1. Introduction

‘Quality of life’ is an important part of clinical evaluation. Health-related quality of life [HRQoL] is a global measure of the patient’s perceptions, illness experience, and functional status, and incorporates social, cultural, psychological, and disease-related factors.3

Crohn’s disease is an incurable inflammatory bowel disease [IBD] characterised by a chronic, relapsing course. Its relatively young age of onset, associated morbidty, disability, debilitating symptoms, and sometimes disfiguring complications have the potential to cause significant psychosocial stress.

Symptoms of active Crohn’s disease such as diarrhoea, abdominal pain, and gastrointestinal bleeding, have been shown in large multinational questionnaire-based studies to have a substantial impact on HRQoL.2–5 It is widely accepted that deterioration in HRQoL and high levels of emotional distress can be observed in patients with active disease.6,7 However even in the absence of active disease, patients with Crohn’s disease report worse HRQoL than those without.8,9,10 Achievement of disease remission, whether by drug therapies [corticosteroids, immunomodulators and/or biologicals] or surgery, is associated with an improvement in HRQoL.12–19

Even in the era of frequent immunomodulator use, including biologicals, patients with Crohn’s disease commonly require surgery.20 HRQoL in patients being referred for surgery is poor22 but does improve following resectional surgery.19,21,22 Ileo-caecal resection, both open and laparoscopic, is associated with significant short-term improvements in HRQoL.19,21,22 However, the long-term durability of improved HRQoL following surgery in these patients is contentious.19,20–22 High rates of clinical and endoscopic recurrence have been shown to affect adversely HRQoL postoperatively in patients with Crohn’s disease.20,22 Recurrent disease, smoking, personality factors, including coping behaviours, and body image disturbance all appear to affect HRQoL after surgery.21,22,27–29

Whether elective surgery with resection for Crohn’s disease is superior to drug therapy in the biological era in terms of symptom control, quality of life, and health economic analysis, is not known. Results from the LYRic-Trial,32 a randomised controlled trial comparing infliximab treatment with laparoscopic ileo-colic resection in patients with recurrent Crohn’s disease of the distal ileum, with respect to quality of life and costs, are not yet available.

Prospective studies to date evaluating HRQoL postoperatively in patients with Crohn’s disease have been small. Whereas most show some improvement in HRQoL, this is not a consistent finding across the literature.18,19,26,27 The effects of strategic prophylactic postoperative drug treatment regimens in improving HRQoL have not been investigated.

This study aimed to determine the changes in HRQoL following intestinal resection of all macroscopic Crohn’s disease in patients treated with selective postoperative immunosuppressive therapy as prophylaxis against disease recurrence. We aimed to determine whether there are specific patient and disease factors or management strategies that can influence HRQoL outcome in this population.

2. Methods

2.1 The clinical postoperative recurrence study

The POCER study was a prospective randomised trial that aimed to assess the value of postoperative endoscopic assessment and treatment step-up for early mucosal recurrence. Patients were stratified according to risk of recurrence. Smokers, patients with perforating disease, or patients with $\geq 1$ previous resections were classified as at ‘high-risk’ of recurrence; all others were deemed ‘low-risk’. All patients underwent resection of all macroscopic disease and then received 3 months of oral metronidazole therapy. High-risk patients also received daily thiopurine in standard dose or adalimumab therapy if thiopurine-intolerant. Low-risk patients received no further medication.

Patients were randomly assigned at study recruitment in a 2:1 ratio to colonoscopy at 6 months [active care] or no colonoscopy [standard care]. The study group allocation sequence was computer-generated with block randomisation undertaken for each centre in blocks of 3 in a 2:1 ratio [2 active care:1 standard care]. Participants were randomised by a computer-generated list maintained centrally. Data analysis was undertaken by statisticians who were not involved in the clinical study and who were blinded to the study groups.

For endoscopic recurrence [Rutgeerts score $\geq i2$] at 6 months [active care arm only], patients stepped-up to thiopurine, fortnightly adalimumab with thiopurine, or weekly adalimumab. The primary end-point was endoscopic recurrence at 18 months. Endoscopic remission was defined as Rutgeerts score i0 or i1 [i0 = no lesions, i1 = mild small superficial anastomotic lesions], and recurrence defined as i2, i3 or i4 [moderate to severe lesions].

All patients provided written informed consent before inclusion in the study. Ethical approval for the study was obtained from the human research ethics committees of the participating hospitals [Clinical Trial Registration: NCT00989560].
2.2 Variables and Measures

The general Short-Form 36 (SF36) and disease-specific Inflammatory Bowel Disease Questionnaire (IBDQ) were used to measure the dependent variable HRQoL. The SF36 is a general, validated, outcome measure which attempts to capture aspects of health that are important to all people. Its use is well established for a wide variety of disease states. The self-questionnaire contains 36 questions subdivided into eight dimensions each of which corresponds to a different aspect of health. Responses are recorded, summed, and transformed to provide the eight dimensions with scores between 0 and 100, with higher scores indicating better health. Scores from the eight dimensions can be aggregated into two summary measures: the Physical [PCS] and Mental [MCS] Component Summary scores (Table 1), also scored from 0 to 100, with higher scores representing better HRQoL. The Australian Bureau of Statistics average SF36 score for each of the eight dimensions is 75–90 in adults without illness, depending on gender, age, income, and smoking status. For individual dimensions of the SF36, a change of 5 or more points is considered to be a minimum important difference.

The IBDQ is the most widely used HRQOL instrument for patients with IBD. The validity, reliability, and responsiveness of the IBDQ have previously been established. The scale has 32 items scored on a 7-point Likert scale, ranging from 1, [worst health] to 7 [best health]. Only the IBDQ total scores were used with a score range of 32 to 224, with higher scores reflecting better HRQOL. A total IBDQ score of ≥ 170 is associated with clinical remission. The IBDQ has previously been established. The SF36, also scored from 0 to 100, with higher scores indicating better health. Scores from the eight dimensions can be aggregated into two summary measures: the Physical [PCS] and Mental [MCS] Component Summary scores. The scale has 32 items scored on a 7-point Likert scale, ranging from 1, [worst health] to 7 [best health].

Patients were asked to complete questionnaires for both the SF36 and IBDQ preoperatively [baseline] and at 6, 12, and 18 months following surgery. In patients who had a diverting ileostomy created at the time of intestinal resection, reversal of the stoma and restoration of the normal faecal stream was considered the index surgery, with postoperative HRQoL assessment performed from this time.

C-reactive protein (CRP), Crohn's Disease Activity Index (CDAI), and faecal calprotectin (FC) were measured at baseline [preoperatively] and postoperatively at 6, 12, and 18 months [within 3 months of delayed follow-up].

2.3 Statistical Analysis

Comparisons between groups were performed using either Kruskall-Wallis or ANOVA [analysis of variance] tests for continuous data and either chi squared or Fisher's exact test for categorical data, as appropriate. Associations between HRQoL and all possible predictors were assessed with analysis of covariance or linear regression. Variables that were found to be associated with quality of life in a univariate analysis were entered into a multivariate regression. Correlation between responses to IBDQ and SF36 questionnaires and clinical and biochemical data were assessed using Spearman's correlation. To enhance statistical power, mean PCS and MCS scores, rather than the individual dimension scores, were used for this analysis. In order to maintain the overall level of significance for the study at 0.05 levels, Bonferroni adjustment was used for individual tests.

Results were expressed as mean and standard deviation [SD] so as to be consistent with the published literature. The distribution of results was approaching normality.

3. Results

A total of 174 patients were included at 17 hospitals in Australia and New Zealand, and completed follow up to 18 months postoperatively. Of 122 patients randomised to endoscopic intervention [6 month colonoscopy], 101 were high-risk, compared with 44 of 56 in the standard care arm [Figure 1]. Demographic details are shown in Table 2. All patients underwent intestinal resection of all macroscopic disease.

Of the 56 patients who withdrew before 18 months [Figure 1], 22 withdrew because of symptom recurrence: 13 [11%] active care vs nine [17%] standard care [p = 0.23]. Median time to withdrawal was 6 months (interquartile range [IQR] 4–12) for the active care group vs 9 months [IQR 9–11] for the standard care group [p = 0.38]. Of 34 withdrawals [24 active care; 10 standard care], 11 were related to comorbidity, 9 to loss to follow-up, 8 to protocol violation, 3 to patient preference, and 3 to pregnancy. An additional 10 patients, who remained enrolled in the study for the duration of the 18 months of follow-up, elected not to complete the quality of life questionnaires at the intervals stipulated in the study design and therefore quality of life data were not available for these patients. There were no differences between patients who did or did not complete the 18-month follow-up with respect to age, sex, smoking status, or other baseline parameters.

Indications for surgery included symptomatic luminal Crohn's disease refractory to standard medical therapy, intestinal obstruction from inflammatory or fibrostenotic disease, or penetrating complications of Crohn's disease, such as abscess formation [Table 2].

A total of 133 patients underwent ileo-caecal resection, 15 simultaneous ileo-caecal and proximal small intestinal resection, 12 ileal resection, 8 subtotal colectomy, and 6 simultaneous ileo-caecal and proximal small intestinal resection. The validity, reliability, and responsiveness of the IBDQ have previously been established. The scale has 32 items scored on a 7-point Likert scale, ranging from 1, [worst health] to 7 [best health]. Only the IBDQ total scores were used with a score range of 32 to 224, with higher scores reflecting better HRQOL. A total IBDQ score of ≥ 170 is associated with clinical remission.

Table 1. Dimensions and components of the SF36.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Component</th>
<th>Dimension</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>PF</td>
<td>Physical Component Summary [PCS]</td>
<td>Physical Functioning</td>
<td>Limitations in physical activities because of health problems</td>
</tr>
<tr>
<td>RP</td>
<td>Role Physical</td>
<td></td>
<td>Limitations in usual role activities because of physical health problems</td>
</tr>
<tr>
<td>BP</td>
<td>Bodily Pain</td>
<td></td>
<td>Intensity of bodily pain or discomfort</td>
</tr>
<tr>
<td>GH</td>
<td>General Health</td>
<td></td>
<td>General Health Perceptions</td>
</tr>
<tr>
<td>VT</td>
<td>Vitality</td>
<td>Social Functioning</td>
<td>Energy and fatigue</td>
</tr>
<tr>
<td>SF</td>
<td>Role Emotional</td>
<td></td>
<td>Limitations in social activities due to physical or emotional problems</td>
</tr>
<tr>
<td>MH</td>
<td>Mental Health</td>
<td></td>
<td>Psychological distress and well-being</td>
</tr>
</tbody>
</table>
sigmoid resection. Surgery was performed laparoscopically in 109 patients; in an additional 17 patients, laparoscopic surgery required conversion to open surgery; and in 48 patients, an open approach was required; 19 patients had a temporary ileostomy created at the time of intestinal resection and ileostomy reversal and restoration of normal faecal transit were completed in all 19 before assessment of postoperative HRQoL.

The main clinical outcomes of the study have been reported previously. In short, a structured programme to prevent postoperative recurrence, with colonoscopic assessment at 6 months and treatment intensification for endoscopic disease recurrence, was significantly superior to optimal drug therapy alone in preventing recurrence at 18 months.

3.1. Quality of life before and after surgery
HRQoL was poor preoperatively when measured by the PCS and MCS scores and the IBDQ [40, 44, and 125, respectively]. There was significant improvement seen at 6 months postoperatively [68, 68, and 171, respectively] \( p < 0.001 \). This improvement was sustained and maintained at 18 months and observed in all measures of HRQoL [Table 3] [Figure 2A and B]. Patients with a temporary

---

**Figure 1.** Consort Diagram: The POCER Study

Patients Screened and Consented
\( n = 212 \)

Surgery

Ineligible After Surgery
\( n = 28 \)

**STRATIFICATION**
\( n = 184 \)

**HIGH RISK**
\( n = 154 \)
One or more of:
- Previous surgery
- Penetrating Disease
- Smoker

**LOW RISK**
\( n = 31 \)
No risk factor

**RANDOMIZATION**
\( n = 184 \)

Did Not Receive Allocated Treatment
\( n = 6 \)

**ACTIVE CARE**
\( n = 128 \)

**STANDARD CARE**
\( n = 56 \)

Did Not Receive Allocated Treatment
\( n = 4 \)

Withdraw Prior to 6 Months
\( n = 18 \)
- 10 Administrative Resources
- 6 Symptom Recurrence
- 2 Comorbidity

Colonoscopy at 6 months
\( n = 104 \)

Rutgeerts score \( i0 \) or \( i1 \)
- No change in therapy

Rutgeerts score \( i2 - i4 \)
- Step-up therapy

Withdraw Between 6 and 18 Months
\( n = 19 \)
- 8 Administrative Resources
- 7 Symptom Recurrence
- 4 Comorbidity

**PRIMARY ENDPOINT**
Colonoscopy at 18 months
\( n = 118 \)
stoma had reduced PCS scores preoperatively when compared with those without a stoma [39 vs 51, \( p = 0.0162 \)] but there were no differences in MCS or IBDQ scores. Postoperatively there were no statistically significant difference in PCS, MCS, or IBDQ scores between those who had had a temporary stoma and those who had not.

### 3.2. Factors affecting quality of life

#### 3.2.1 Gender

For the SF36, preoperative differences between men and women were statistically significant for the PCS \( [p = 0.029] \), but not for the MCS \( [p = 0.160] \) scores.

For the IBDQ, the differences between men and women in preoperative HRQoL were not statistically significant \( [p = 0.062] \).

Postoperatively, HRQoL was higher in men for the MCS and PCS scores and the IBDQ score when compared with women. Differences reached statistical significance for the PCS and MCS scores at 6 months \( [p = 0.017 \) and \( p = 0.015 \), respectively]; and at 12 months \( [p < 0.001 \) and \( p = 0.006 \), respectively]; but not at 18 months \( [p = 0.121 \) and \( p = 0.485 \), respectively] [Figure 3A and B]. When measured by the IBDQ, statistically significant differences were seen between males and females at 6 and 12 months \( [p = 0.007 \) and \( p = 0.006 \), respectively] [Figure 3C].

#### 3.2.2 Smoking

Smokers had a lower HRQoL compared with non-smokers. Differences reached statistical significance postoperatively for PCS

---

**Table 2. Patient demographics.**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Active care</th>
<th>Standard care</th>
<th>Overall p-value active care vs standard care</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>No. [male]</td>
<td>51</td>
<td>51</td>
<td>8</td>
</tr>
<tr>
<td>Age &gt; 40 years</td>
<td>42</td>
<td>42</td>
<td>9</td>
</tr>
<tr>
<td>Age, median</td>
<td>36</td>
<td>34</td>
<td>36</td>
</tr>
<tr>
<td>Age at diagnosis [years]</td>
<td>≤16 Years [A1]</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>17–40 Years [A2]</td>
<td>79</td>
<td>78</td>
</tr>
<tr>
<td></td>
<td>&gt;40 Years [A3]</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>≥10 years</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Disease location at surgery</td>
<td>Ileum only [L1]</td>
<td>51</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td>Colon only [L2]</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Illeum and colon [L3]</td>
<td>44</td>
<td>44</td>
</tr>
<tr>
<td>Disease phenotype at surgery</td>
<td>Inflammatory [B1]</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Strictureing [B2]</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>Penetrating [B3]</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>Indication for surgery</td>
<td>Failure of drug therapy</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Obstruction</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>Perforation</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>Surgical technique</td>
<td>Open</td>
<td>36</td>
<td>35·6</td>
</tr>
<tr>
<td></td>
<td>Laparoscopic</td>
<td>56</td>
<td>55·4</td>
</tr>
<tr>
<td></td>
<td>Conversion [laparoscopic to open]</td>
<td>9</td>
<td>8·9</td>
</tr>
<tr>
<td>Surgical complications</td>
<td>Any postoperative complication</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

**Table 3. HRQoL before and after surgery.**

<table>
<thead>
<tr>
<th>HRQoL measure</th>
<th>Summary score</th>
<th>Preoperatively mean [SD]</th>
<th>Postoperatively [months]</th>
<th>Significance of postoperative change, p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=165</td>
<td>n=148</td>
<td>n=121</td>
<td>n=108</td>
</tr>
<tr>
<td>SF-36 [0–100]</td>
<td>PCS [0–100]</td>
<td>40 [21]</td>
<td>68 [21]</td>
<td>71 [20]</td>
</tr>
<tr>
<td></td>
<td>MCS [0–100]</td>
<td>44 [22]</td>
<td>68 [20]</td>
<td>70 [19]</td>
</tr>
<tr>
<td>IBDQ [32–224]</td>
<td></td>
<td>125 [35]</td>
<td>171 [33]</td>
<td>175 [31]</td>
</tr>
</tbody>
</table>

HRQoL, health-related quality of life.
and MCS scores at 12 months \( p = 0.002 \) and \( p = 0.002 \), respectively, and the MCS score at 18 months \( p = 0.033 \). When measured by the IBDQ, statistically significant differences in HRQoL were seen postoperatively at 12 months \( p = 0.046 \) and 18 months \( p = 0.047 \).

### 3.2.3 Disease duration
Disease duration did not appear to affect HRQoL in our population. There were no statistically significant differences in HRQoL pre- or postoperatively when measured by SF36 or IBDQ between those with a disease duration > 10 years when compared with those with a disease duration of ≤ 10 years.

### 3.2.4 Perianal disease
Perianal disease was present in 12% of patients preoperatively and in 11% postoperatively. Both preoperatively and postoperatively, HRQoL did not appear to be affected by the presence of perianal disease, with no statistically significant differences seen in the PCS, MCS, or IBDQ scores between those with and without perianal disease.

### 3.2.5 CDAI
There was a significant inverse relationship between CDAI and HRQoL when measured by both the SF-36 and IBDQ. Statistically significant differences in the PCS, MCS, and IBDQ scores were seen...
Figure 3. Gender differences in health related quality of life (HRQoL) pre-operatively and post-operatively at 6, 12 and 18 months. Figures 3A and 3B show the physical (PCS) and mental (MCS) Component Summary scores of the SF36 with respect to gender. Figure 3C shows scores for the IBDQ with respect to gender.
between those with a CDAI < 150, CDAI 150–219 and CDAI > 220, both pre and postoperatively [Table 4].

3.2.6 CRP
An elevated CRP [≥ 5 mg/l] was associated with a lower MCS score at baseline [p = 0.039]. Postoperatively elevated CRP was associated with significant reduction in the PCS score [p = 0.026] but not MCS [p = 0.098] or IBDQ scores [p = 0.289].

3.2.7 Faecal calprotectin
There were no statistically significant differences in quality of life between those with a FC < 100 µg vs FC ≥ 100 µg when measured by the SF36 or IBDQ.

3.2.8 Active care arm
There were no significant differences seen in HRQoL between patients in the active care arm of the POCER study, when compared with those in the standard care arm when measured by SF36 and IBDQ, both pre- and postoperatively.

3.2.9 Endoscopic remission
Endoscopic remission [Rutgeerts i0 or i1] at either 6 or 18 months was not associated with a different HRQoL compared with patients not in endoscopic remission [Rutgeerts i2, i3 or i4] when measured by SF36 or IBDQ.

3.2.10 Treatment step-up
Intensification of drug therapy at 6 months, in those in the active care arm who had endoscopic recurrence [Rutgeerts i2, i3, or i4] on colonoscopy, was not associated with a statistically significant change in HRQoL [when measured by both SF36 and IBDQ] at 12 or 18 months postoperatively when compared with those with endoscopic remission at 6 months who did not receive treatment intensification.

3.2.11 Adalimumab therapy
Patients who received adalimumab therapy postoperatively did not have a different HRQoL compared with those who did not at 6, 12, or 18 months.

3.2.12 Surgical technique
The quality of life outcome did not differ according to the surgical technique [open vs laparoscopic vs laparoscopic converted to open].

3.2.13 Postoperative complications
A total of 29 patients reported complications, with 20 having 34 of the predefined complications [including wound infection, wound dehiscence, abdominal collection/abscess, anastomotic leak, and return to theatre]; 9 reported other complications [data not provided]; 55% pre-defined complications in each group were related to wound infection.

Patients who experienced a postoperative complication did not have a significantly different HRQoL compared with those who did not, postoperatively.

3.3 Correlation analysis
The PCS and MCS scores both correlated significantly with the IBDQ. CDAI correlated significantly with the IBDQ total score [r = -0.5046, p = 0.0049]. There was no correlation seen between Rutgeerts endoscopic score, CRP, or FC and quality of life measures.

### Table 4
HRQoL, health-related quality of life; CDAI, Crohn's Disease Activity Index.

<table>
<thead>
<tr>
<th>HRQoL measure</th>
<th>Summary score</th>
<th>Preoperatively, CDAI [SD]</th>
<th>Postoperatively, CDAI [SD]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>SF-36</td>
<td>PCS [0–100]</td>
<td>6 CDAI &lt; 150</td>
<td>150–219</td>
<td>&gt; 220</td>
</tr>
<tr>
<td></td>
<td>05 [0–100]</td>
<td>05 [0–100]</td>
<td>05 [0–100]</td>
<td>05 [0–100]</td>
</tr>
<tr>
<td></td>
<td>IBDQ [32–224]</td>
<td>05 [0–100]</td>
<td>05 [0–100]</td>
<td>05 [0–100]</td>
</tr>
<tr>
<td></td>
<td>05 [0–100]</td>
<td>05 [0–100]</td>
<td>05 [0–100]</td>
<td>05 [0–100]</td>
</tr>
</tbody>
</table>

**Effect of Surgery on Quality of Life in Crohn's**
4. Discussion

Numerous physical and psychological factors contribute to the poor HRQoL in patients with Crohn’s disease. Long-term drug treatment and the need for surgery have measurable effects on both individual patients and society. Collection of HRQoL data provides insight into the impact of treatment on patient health status and well-being.

Of the 80% of patients with Crohn’s disease who will require bowel surgery at some time in their life, up to 70% will require a second operation.67 Prior to the routine use of immunomodulators and biologicals for moderate to severe Crohn’s disease, surgery was used early and frequently as part of disease management and was efficacious in terms of symptom relief, and successful restoration of 90% of patients to good or excellent health.48

Even in the era of routine immunosuppressive therapy for moderate to severe Crohn’s disease, the need for surgery remains high.20 HRQoL in patients being referred for surgery is poor18 but improves following resectional surgery.19,21,22 However, these improvements may not be durable, mainly because of the high rates of clinical and endoscopic recurrence which have been shown to adversely affect HRQoL postoperatively in some studies.26,27 Small studies have found that there may be a sustained improvement in HRQoL after surgery. Thirlb and colleagues,19 in their study of 56 Crohn’s disease patients having resectional surgery, demonstrated durable improvement in postoperative quality of life when compared with their preoperative status after a mean of 16 [3–76] months. Thirlb et al. demonstrated that postoperative HRQoL, measured using the Health Status Questionnaire [HSQ], was comparable to the quality of life in the general population.

The durability of any improvement in HRQoL following intestinal resection has not been examined in a population receiving prophylactic drug therapy and rigorous postoperative monitoring. The strategic approach, with a focus on maintaining remission, in our study was associated with significant and sustained improvements in general and disease-specific HRQoL. Of the many patient, disease, and treatment factors examined, only gender, smoking status, and CDAI were associated with consistent differences in postoperative HRQoL.

There was no difference in HRQoL in patients in the standard vs active care groups, despite the differences in endoscopic recurrence rates at 18 months.46 This is likely to be a reflection of the absence of a significant difference in clinical recurrence [CDAI > 150] rates between the active and standard care groups at 18 months and the fact that CDAI does not correlate with endoscopic recurrence after ileo-colonic resection.41 It is possible that, with extended follow-up, differences between the two groups would emerge as patients with endoscopic recurrence become symptomatic.

Elevated CRP postoperatively was not found to be reliably or persistently associated with poor HRQoL. This result is likely to reflect both the poor performance of CRP as an indicator of clinically or endoscopically active Crohn’s disease and the largely subjective nature of quality of life questionnaires.

The significantly lower PCS score preoperatively, and lower PCS, MCS, and IBDQ scores postoperatively, in female patients when compared with males may reflect the partly lower quality of life reported in healthy female and female IBD populations.30–33 Specific female concerns regarding interpersonal relationships and sexual comfort, behavior, and functioning may play a role but this requires further investigation. The association of psychiatric comorbidity and stress with HRQoL in patients with IBD is well established.36–39

Depressive disorders and anxiety are more common in women than men and this is likely to be a significant factor in determining HRQoL in patients with and without IBD.60,61

In this study smoking was associated with a lower HRQoL postoperatively. Smoking has been consistently reported across the literature as being associated with aggressive disease, poor outcomes and higher rates of surgical therapy in Crohn’s disease.62–64 Smoking also appears to be associated with lower QoL scores in patients with Crohn’s disease.51,53,54 In the POCER study smoking was associated with a significant increase in the risk of endoscopic recurrence [OR 2.4, 95% CI 1.2–4.8, p=0.02] confirming a more aggressive disease phenotype in these patients.46 However endoscopic recurrence was not associated with a worse HRQoL in this study indicating that non-disease factors may be responsible for the lower quality of life reported by smokers in this study.

A higher clinical disease activity index, but not direct measures of active disease, such as CRP, FC, or endoscopic recurrence, was associated with a lower HRQoL. This suggests that symptoms, which are directly measured in the CDAI, reflect subjective personal factors and not active mucosal disease or drug effects. Further questions reflecting bowel symptoms and general well-being, which form part of the CDAI, are also part of the IBDQ; a close correlation between the CDAI and quality of life measures is therefore expected.

Comparing the magnitude of benefit in quality of life following resectional surgery to other interventions is difficult as there are no direct comparative studies. However we can examine the effect of anti-TNF therapies and small molecules on quality of life Crohn’s disease as described in the pivotal trials of these drugs and compare the changes in quality of life to those we observed in our postoperative cohort. Targan et al.67 demonstrated significant improvement in HRQoL as measured by IBDQ after four weeks of infliximab therapy in patients with moderate to severe Crohn’s disease [IBDQ 122 to 168, P<0.001] an increase in IBDQ of 46 points. No significant difference at four weeks was seen in patients treated with placebo [IBDQ 128 and 133]. Similar improvements have been observed in other large clinical trials of both Infliximab and Adalimumab.67,68 The Study of Biologic and Immunomodulator Naive Patients in Crohn’s Disease [SONIC] trial found that patients treated with infliximab containing regimens [either as monotherapy or combined with azathioprine] had a significantly greater change in HRQoL compared to patients treated with azathioprine alone.69 At 26 weeks there was a mean change in IBDQ from baseline of 31.4, 39.9 and 45.2 for the three groups respectively. Vedolizumab, an α4β7 integrin antagonist, has been shown to induce remission by 6 weeks in more patients compared to placebo.70 There was no clear improvement however in the IBDQ-measured QoL with maintenance vedolizumab therapy [whether given every 4 or 8 weeks].

The magnitude if improvements in HRQoL seen with both infliximab, adalimumab and combination infliximab and azathioprine are similar to what we have observed postoperatively in this study where an increase in IBDQ of 46 points was seen at 6 months postoperatively when compared to baseline.

In conclusion, this study has shown that intestinal resection of all macroscopic Crohn’s disease followed by prophylactic drug therapy with a focus on maintaining remission, is associated with significant and durable improvement in general and disease-specific HRQoL. This improvement is sustained at 18 months post operatively, irrespective of endoscopic recurrence or the type of drug therapy. Women and smokers appear to have lower quality of life, despite removal of all active disease, suggesting that non-disease factors should receive attention in these patients.
Acknowledgements

Abbvie, Gutsy Group, Gandel Philanthropy, Angior Foundation, Crohn’s Colitis Australia and St Vincent’s Research Endowment Fund provided research support. The National Health and Medical Research Council [NHMRC] supported EKW, PDC, RWL and MAK. We are grateful to colleagues and centres for their participation.

EKW, PDC and MAK – study concept and design; acquisition of data; analysis; data interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding. ALH – acquisition of data; analysis and interpretation of data; drafting of the manuscript. KJR and EOK – acquisition and monitoring of data. AG and DL – analysis and interpretation of data; drafting of the manuscript; statistical analysis. LP, JMA, PAB, MPS, THF, PRG, HD, ASH, RBB RWL, FAM, IK, GRS, WS, MJJ, RW, RE, SJB, SJB, WRC, PVD – acquisition of data and critical review of manuscript for important intellectual content.

Conflict of interest statement

EK Wright, KJ Ritchie, EO Krejany, A Gorelik, L Prideaux, TH Florin, H Debinski, 1 Kronborg, MJ Johnston, R Woods, PR Elliott and PV Desmond have no conflicts of interest to declare. P De Cruz has received travel grant support from Abbvie and Schering-Plough. MA Kamm has acted as an advisor to Abbvie and Janssen, has received research support from Abbvie, and has acted as a speaker at symposiums sponsored by Abbvie and Janssen. A Hamilton has received an educational grant from Abbvie. D Liew has served on advisory boards and received research grants from Abbvie. IC Lawrence has been on an advisory board for Abbvie and Janssen, a speaker for Abbvie and Janssen, and has held research and travel grants from Abbvie and Janssen. JM Andrews has been an advisory board member for both Janssen and Abbvie, spoken for both Abbvie and Janssen, received research funds from both Abbvie and Janssen, and received travel grants from both Abbvie and Janssen. PA Bampton has been on advisory boards for Janssen and Abbvie, has received research funding from Abbvie, and travel sponsorship from both Abbvie and Janssen. MP Sparrow has been on the advisory board for Janssen and received speakers fees from Janssen and Abbvie. PR Gibson has received consulting fees from Abbvie, Janssen, and Schering-Plough; research support from Abbvie; and payments for lectures from Abbvie and Janssen. RB Garry has been on an advisory board for Abbvie and Janssen, a speaker for Abbvie and Janssen, and held research, educational and travel grants from Abbvie and Janssen. FA Macrae has been on an advisory board to Janssen, has received travel grants from Abbvie, and has received clinical research support from Janssen, Abbvie and MSD. RW Leong has served on advisory boards for Abbvie and Janssen. G Radford-Smith has served on advisory boards for Abbvie and Janssen. W Selby has been on an advisory board for Abbvie. SJ Bell has received travel assistance from Abbvie. SJ Brown has received travel support and speaker fees from both Abbvie and Janssen. WR Connell has been on advisory board for Janssen and a speaker for Abbvie and Janssen.

References


