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Longitudinal quality of life and quality adjusted survival in a randomised controlled trial comparing six months of bolus fluorouracil/leucovorin *vs.* twelve weeks of protracted venous infusion fluorouracil as adjuvant chemotherapy for colorectal cancer

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Abstract

Longitudinal quality of life (QOL) assessment is infrequently made in adjuvant therapy for colorectal cancer (CRC). This analysis aims to assess QOL and quality adjusted survival (QAS) in patients receiving adjuvant 5-FU for stage II and III CRC. We performed a multicentre study in which 801 patients were randomised to 6 months of bolus 5-FU/leucovorin (LV $n = 404$) or 12 weeks of protracted venous infusion (PVI) 5-FU ($n = 397$). There were significant differences in the deterioration of QOL scores at week 2 with bolus 5-FU/LV compared to PVI 5-FU ($P < 0.001$), coinciding with toxicity peak during the first cycle. Following week 12, global QOL recovered to baseline when PVI 5-FU was stopped but this was delayed with bolus 5-FU/LV until completion at week 24. QOL scores significantly improved in both arms during follow-up ($P < 0.001$) and reached a plateau by year 1 without incremental improvement between years 2 and 5. There was a trend towards better QAS with PVI 5-FU. Twelve weeks of adjuvant PVI 5-FU was associated with significantly better QOL during treatment and faster time to recovery compared to 6 months of bolus 5-FU/LV.

Keywords: Colorectal cancer; Adjuvant therapy; Quality of life; 5-FU infusion

1. Introducton

Adjuvant chemotherapy, with or without radiotherapy (RT), is often advocated in patients with high risk stage II or stage III colorectal cancer (CRC). Yet quality of life (QOL) is infrequently assessed in randomised

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controlled trials of adjuvant therapy in CRC. Most studies, although not many, only measured QOL up to 2 years post-treatment. Health related QOL data on long-term survivors have been assessed in a few studies [1–5], but most were cross-sectional studies without baseline (post-surgery) and longitudinal QOL assessment.

Quality-adjusted survival analysis is based on the concept of quality-adjusted life years (QALYs) where both quality and quantity of survival are combined into a composite measure. The Quality-adjusted Time Without Symptoms or Toxicity (Q-TWIST) method is one of the most widely used QALY models to evaluate the balance between treatment toxicity and improved QOL associated with delayed recurrence and increased survival [6]. Periods of survival time spent with symptoms of disease and toxicity resulting from treatment are each given weights between 0 and 1. The periods of time in various health states in a Q-TWIST model are generally determined using clinical outcomes collected in trials. However, such health-state models are unhelpful when the transitions between health states are unclear or if they do not adequately reflect variations in QOL. An alternative analysis can be used when repeated measures of QOL are available from individual patients in a clinical trial. The method proceeds by separating quality of life and survival, i.e., $dQALY/dt = S(t)Q(t)$ where $S(t)$ is the survival curve, estimated from the standard Kaplan–Meier method and $Q(t)$ is the QOL function, derived from individual repeated measures of QOL [7].

Between 1993 and 2003, we conducted a multicentre prospective randomised study comparing the efficacy of protracted venous infusion (PVI) 5-FU with bolus 5-FU/leucovorin (LV) as adjuvant therapy in patients with potentially curative resected colorectal cancer. The primary efficacy data with a median follow-up of 5.25 years is the subject of a separate publication [8]. In brief, PVI 5-FU was associated with a trend towards better relapse-free [Hazard ratio (HR): 0.8; 95% confidence interval (CI): 0.62–1.04; $P = 0.10$] and overall survival (HR: 0.79; 95% CI: 0.61–1.03; $P = 0.083$) compared to bolus 5-FU/LV. Based on our results, the probability of 12 weeks of PVI 5-FU being inferior to 6 months of bolus 5-FU/LV is extremely low ($P < 0.005$). Significantly reduced incidences of neutropenia, diarrhea, stomatitis, nausea and vomiting, alopecia and lethargy (all with $P < 0.0001$), anaemia ($P = 0.019$) and thrombocytopenia ($P = 0.025$) were seen with PVI 5-FU. Hand foot syndrome was, however, more frequent ($P < 0.0001$) compared to bolus 5-FU/LV. Here, we report on the longitudinal QOL data on patients in this trial and the incorporation of these data in a quality-adjusted survival analysis.

2. Patients and methods

Patients were entered into the study within 12 weeks of curative resection of stage II and III adenocarcinoma of the colon or rectum. Before randomisation, post-operative CT scan of thorax, abdomen and pelvis as well as carcinoembryonic antigen (CEA) measurement were performed to exclude previously unsuspected metastatic disease or development of metastatic disease post-operatively. Surgical specimens or representative slides were reviewed in the histopathology department to confirm tumour stage and resection margin status. Resection margins were required to be clear by at least 1 mm in all patients. Patients were required to have adequate haematological, renal and liver function and no concurrent severe or life threatening illness. Pre-operative RT was allowed in patients with rectal cancer. Participating patients gave written informed consent before they entered the study. The protocol was approved by the Scientific and Research Ethics Committee of the institutions taking part as well as the London Multicentre Research Ethics Committee.

Details of all eligible patients were forwarded to the trial office based at the Royal Marsden Hospital, Surrey, UK to verify eligibility criteria. Patients were then randomly assigned by an independent randomisation office to either bolus 5-FU/LV or PVI 5-FU on a 1:1 basis using random permuted blocks. Randomisation was stratified by treatment centre and in cases of rectal cancer whether pre-operative RT was given.

Patients were randomly allocated to PVI 5-FU given at a dose of 300 mg/m^2/day for 12 weeks (PVI 5-FU arm) or bolus 5-FU (425 mg/m^2) and LV (20 mg/m^2) on days 1–5 every 4 weeks for six cycles (5-FU/LV arm). Patients, aged over 70 and allocated to the bolus 5-FU/LV arm, were treated with a reduced starting dose of 370 mg/m^2. Adjuvant radiotherapy was reserved for those patients at high risk of locoregional failure (T4 tumours), and was planned to start with the fourth cycle of bolus therapy or after completion of 12 weeks of PVI 5-FU which continued at a reduced dose of 200 mg/m^2 until completion of radiotherapy.

Quality of life (QOL) assessment was made using the European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ C-30) version 1. This is a validated 30-item questionnaire consisting of five functional scales, three symptom scales and one global health status scale [9]. Five single items assessed additional symptoms including appetite loss and diarrhea. For functional scale, high score indicated better QOL whereas for symptom scales high score indicated more symptoms and poorer QOL.

QOL assessment was made before randomisation, at weekly interval in the first month, 2-weekly interval until end of treatment, 1 month post-treatment and at week 24 (i.e., 4 weeks after the last dose of bolus 5-FU/LV),

then at every follow up clinic visit. Patients were seen in the out-patient clinic every 3 months for the first year, every 6 months for the second year and annually thereafter up to 5 years. As the duration of treatment was different between the two arms, more frequent assessment was made in the first four months to capture the effect of toxicity on quality of life in either arm. The QOL questionnaire were administered by research nurse and filled in by individual patients. Every effort was made to administer the questionnaire prior to consultations with the clinicians.

3. Statistical considerations

Quality of life scores collected from the EORTC QLQ c30 were linearly transformed to a scale of 0–100 according to EORTC guidelines. For quality of life assessment, the primary analysis was the comparison between treatment arms (bolus 5-FU/LV *vs.* PVI 5-FU). Secondary analyses set *a priori* were the comparisons between genders (male *vs.* female), age (<70 *vs.* $\geqslant$70) and primary tumour location (colon *vs.* rectum). The mean changes in raw linearly transformed score or mean changes from baseline QOL score in all domains were calculated and shown graphically with their confidence intervals (CI). Mean QOL scores were compared using the Mann–Whitney test.

The survival function was estimated using the Kaplan–Meier method [10]. Overall survival was calculated from the date of randomisation to death from any cause or censored at the last follow-up. Survival was expressed as a proportion. Quality adjusted survival analysis was performed by combining longitudinal quality of life data with survival data at a group level (integrated QOL- survival product) using the following formula:

$$\mathrm{QALY}(L) = \int_0^L Q(t)S(t)\,\mathrm{d}t.$$

The survival function $S(t)$ was multiplied by the quality of life function $Q(t)$ for the group, where $S(t)$ was the proportion of subjects that survive to time t and $Q(t)$ is the quality of life of those survivors. In this way, a quality adjusted survival curve was created for the group. The area under this curve up to the time L (5 years) gave the mean QALY for the group for this period [11].

We calculated 5-year QALY in our study for each functioning domain of the EORTC QLQ c-30. The standard error for the mean QALY (L) was estimated by a bootstrapping method [12] enabling CIs to be calculated and hypothesis tests to be carried out. Bootstrapping was carried out 5000 times for each mean QALY (L). For quality adjusted survival, the primary analysis was the comparison between treatment arms. Secondary analyses set *a priori* were the comparison between gender (male *vs.* female), age (<60 *vs.* 60–69 *vs.* 70), performance status (0 *vs.* 1–2), primary tumour location (colon *vs.* rectum), N stage (II *vs.* III) and T stage (T1–2 *vs.* T3–4).

All analyses were performed on an intension-to-treat basis using SPSS version 12 (SPSS Inc. Chicago). As multiple statistical analyses were conducted, two-sided P values <0.01 were considered to be significant.

4. Results

Between 1993 and 2003, 801 eligible patients were recruited from nine oncology centres and randomly allocated to bolus 5-FU/LV arm ($n = 404$) or PVI 5-FU arm ($n = 397$). The median follow-up of the survivors was 64 months. The baseline characteristics were well balanced between the two treatment arms and were fully described in a separate publication [8]. For the patients with rectal cancer ($n = 323$), 237 (73.4%) had an anterior resection, 82 (25.4%) had abdomino-pereneal (AP) resection or Hartmann's procedure and the surgical procedure was unknown in 4 (1.2%) patients.

In total, 9607 QOL questionnaires were returned from patients randomised to bolus 5-FU/LV ($n = 5163$) and PVI 5-FU ($n = 4444$). Fig. 1(a) shows the changes in global health status QOL from baseline by treatment arms. There was a significant difference in the deterioration of QOL scores at week 2 with bolus 5-FU/LV compared to PVI 5-FU. Following week 12, global QOL recovered to baseline when PVI 5-FU was stopped, but this was delayed with bolus 5-FU/LV until completion at week 24. QOL scores significantly improved in both arms during follow-up compared to baseline ($P < 0.001$). This improvement in QOL reached a plateau at year 1 with no significant increment between years 2 and 5.

Table 1 shows the differences in quality of life scores from baseline by treatment arm. Apart from global health status QOL, similar trends were also seen in physical, role and social functioning domains. For the emotional domain, although there was no significant decrease from baseline with treatment, patients in both arms improved significantly from baseline during follow-up. Cognitive functioning also reduced significantly during treatment. Whereas patients in the PVI 5-FU arm retuned to baseline by week 14, patients in the bolus arm only did so after one year. In addition, no significant improvement from baseline was seen in either arm during follow-up.

As shown in Table 1, treatment induced worsening of nausea and vomiting ($P < 0.001$), diarrhoea ($P < 0.001$), fatigue ($P = 0.006$) and appetite ($P < 0.001$) occurred more significantly in bolus 5-FU/LV arm during peak toxicity phase (i.e., week 2). In the bolus 5-FU/LV arm, the pain score rose significantly from baseline during peak toxicity phase ($P < 0.001$) possibly related to stomatitis or abdominal cramps from diarrhoea, then pain resolved with supportive measures and 5-FU dose

reduction. Interestingly, constipation was also worse in the bolus 5-FU/LV arm possibly related to overzealous supportive measure of diarrhoea. Both nausea and vomiting and diarrhoea were worse for bolus 5-FU/LV arm throughout treatment phase, but both symptom scores returned back to baseline during follow-up. Whereas most of the symptom scales returned to baseline during follow-up, there was a significant improvement in fatigue score during follow-up compared to baseline ($P < 0.001$). Interestingly, low-grade dyspnoea occurred in both arms and persisted throughout treatment and follow-up. Perception of financial QOL significantly improved during follow-up compared to baseline in both treatment arms.

In the comparison between genders, females had significantly worse physical ($P < 0.001$), role ($P = 0.008$), emotion ($P < 0.001$), appetite ($P = 0.001$) and fatigue ($P < 0.001$) scores at baseline compared to males. In the comparison between age groups, the $\geqslant 70$ years age group had worse physical functioning ($P = 0.008$), but better role ($P = 0.004$) and social ($P < 0.001$) functioning at baseline. Apart from financial perception ($P < 0.001$), there were no differences in baseline symptom scores between the age groups.

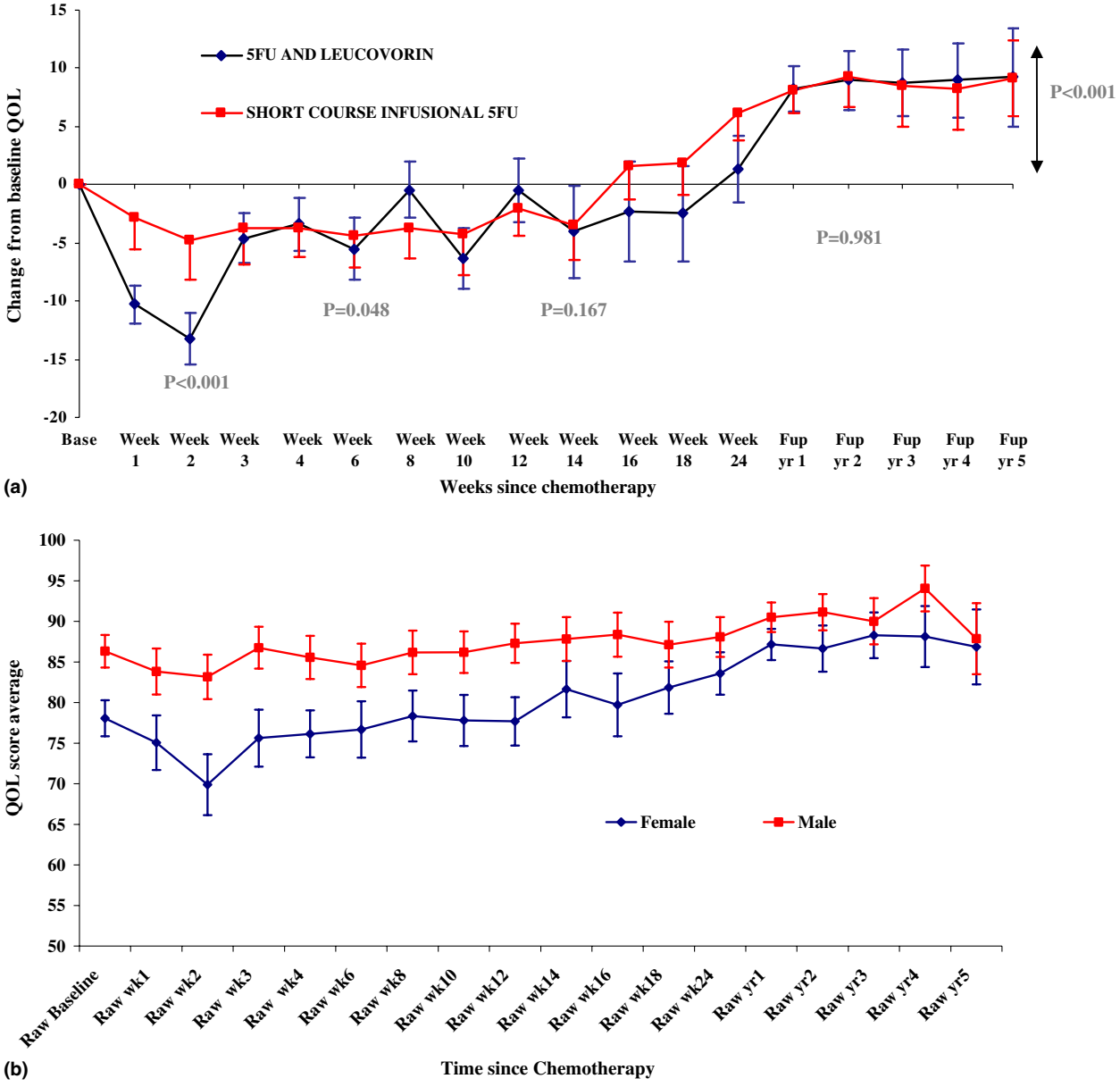

Fig. 1. Quality of life scores relating to treatment arms and patient characteristics (a) changes of global health status quality of life from baseline by treatment arms, (b) QOL comparing physical functioning by gender, (c) QOL comparing physical functioning by age group and (d) comparison of global health status quality of life by tumour location. QOL, quality of life; Base, baseline; Fup, follow-up; Raw, absolute linearly transformed score in QOL; wk, week; yr, year.

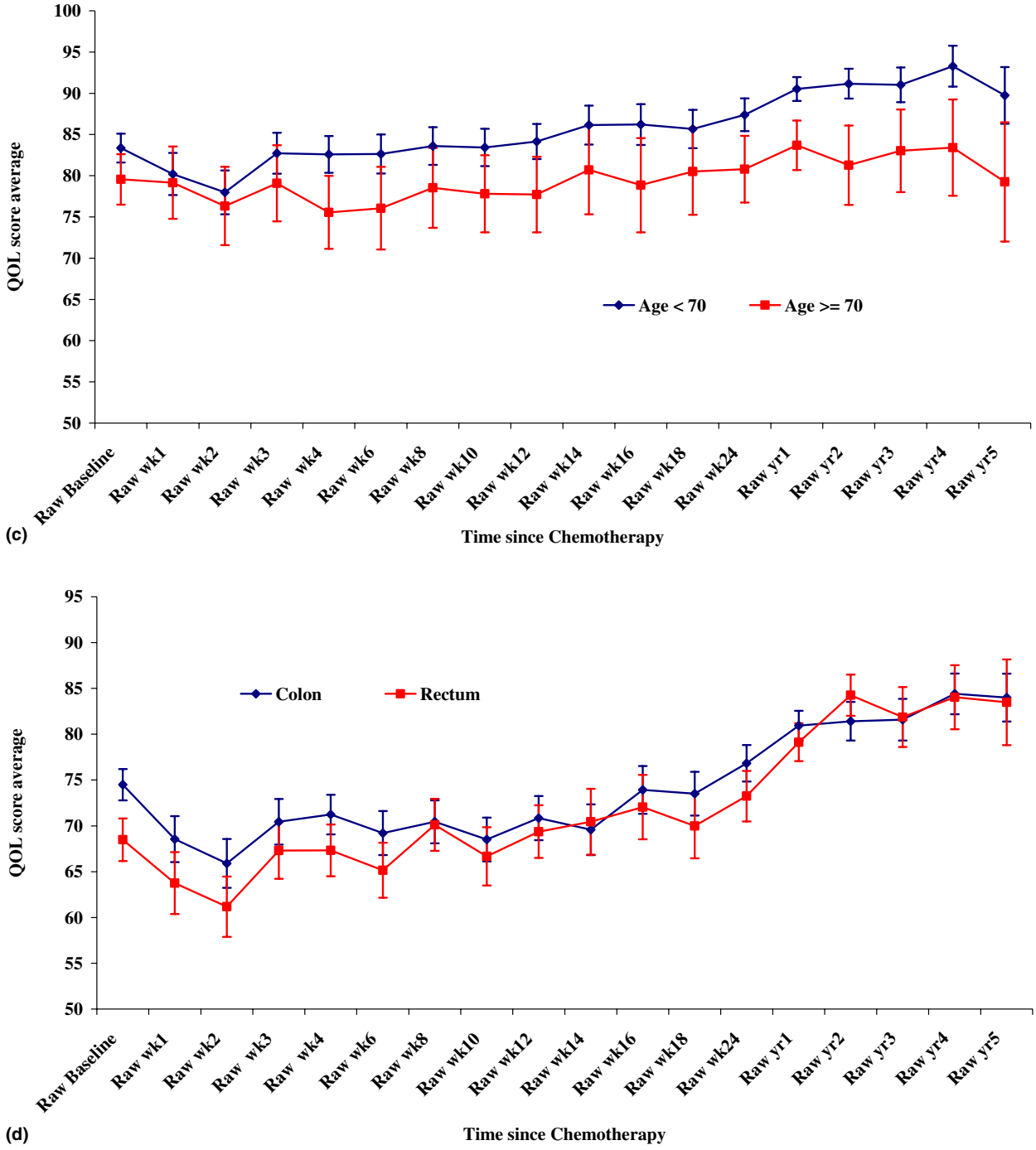

Fig. 1 (*continued*)

In the comparison between anatomical locations, patients with rectal cancer had a significantly worse role ($P < 0.001$) and global ($P < 0.001$) functioning as well as fatigue ($P = 0.007$) at baseline. Notably pain ($P = 0.725$) and diarrhoea ($P = 0.907$) were not worse in rectal cancer patients. During treatment, toxicity causes similar magnitude of effects on functioning and symptoms irrespective of gender, age and tumour location. During follow-up, younger patients had a significant improvement in fatigue, pain and financial perception compared to baseline. However, whereas the QOL score for the $\geqslant 70$ years age group merely returned to baseline, there were significant improvements in the <70 year old age group in physical, role, emotion, social and global QOL compared to the baseline ($P < 0.01$). Average QOL scores relating to patient gender, age and tumour location are shown in Fig. 1(b)–(d)

Table 1
Quality of life differences from baseline by treatment arm

Differences from baseline	Two weeks post-randomisation			Two years post-randomisation		
QOL parameters	Bolus 5-FU/LV	PVI 5-FU	*P*-value	Bolus 5-FU/LV	PVI 5-FU	*P*-value
Physical function	−8.5[a]	−4.4[a]	0.093	+5.8[a]	+4.9[a]	0.832
Role function	−7.6[a]	−4.2	0.531	+10.4[a]	+10.1[a]	0.925
Emotional function	−1.6	+0.5	0.374	+4.3[a]	+7.5[a]	0.064
Cognitive function	−7.1[a]	−1.8	0.04	−0.95	+0.94	0.123
Social function	−7.1[a]	−1.4	0.02	+10.5[a]	+15.6[a]	0.063
Global health status	−13.2[a]	−4.8[a]	<0.001	+9.0[a]	+9.3[a]	0.999
Diarrhoea	+21.4[a]	+5.3[a]	<0.001	−0.3	−1.4	0.346
Nausea and vomiting	+9.0[a]	+2.5	<0.001	−1.4	−0.2	0.203
Fatigue	+12.1[a]	+5.0[a]	0.006	−8.1[a]	−11.2[a]	0.26
Appetite	+16.6[a]	+0.7	<0.001	−3.6[a]	−2.4[a]	0.403
Pain	+8.1[a]	+2.4	0.075	−6.2[a]	−4.2[a]	0.256
Dyspnoea	+3.3[a]	+4.5[a]	0.289	+2.1	+3.8[a]	0.624
Sleep	+3.5	−0.1	0.196	−7.3[a]	−5.8[a]	0.295
Constipation	+4.4[a]	−1.0	0.022	0.2	−1.4	0.631
Financial	+1.9	+0.5	0.254	−3.0	−4.7[a]	0.301

LV, leucovorin; for functional scores, the lower the scores the worse the quality of life was; for symptom scores, the higher the scores the worse the quality of life was; *P*-values refer to the differences between the two treatment arms.
[a] Significantly different from baseline $P < 0.01$.

In a multivariate analysis on overall survival, the significant poor prognostic factors were stage III ($P < 0.00001$), T4 ($P = 0.0066$), male ($P = 0.0352$), performance status 1–2 ($P = 0.0064$) and a prolonged (>8 weeks) interval between surgery and starting adjuvant chemotherapy ($P = 0.0293$). Treatment arm

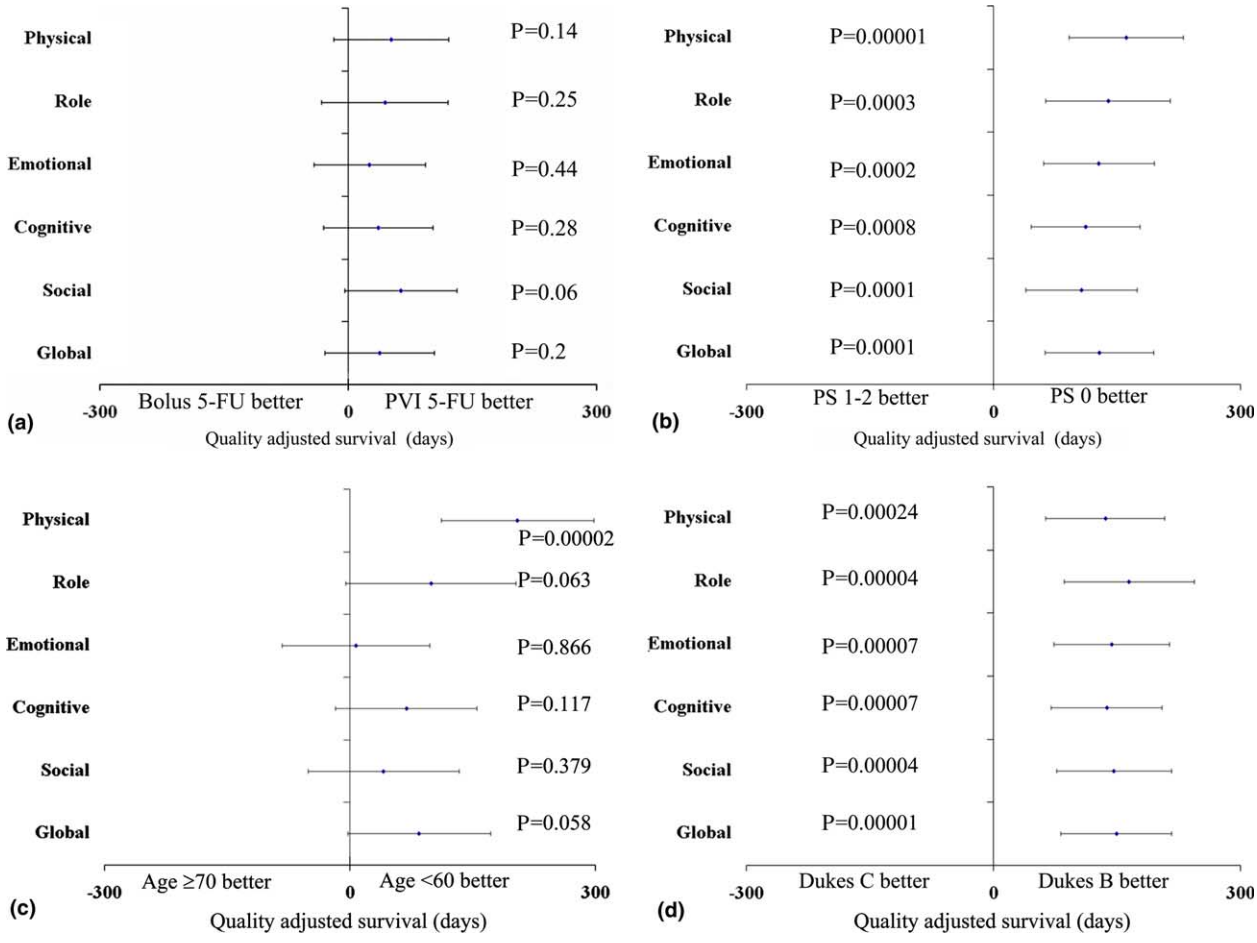

Fig. 2. Comparison of quality adjusted survival by: (a) treatment arms, (b) performance status, (c) age group and (d) nodal stage.

did not significantly influence survival ($P = 0.0759$). Fig. 2(a) shows the quality adjusted survival comparison between treatment arms. In all functioning domains and global health status, there were trends in favour of PVI 5-FU, but none had reached statistical significance. Figs. 2(b)–(d) shows the QAS comparisons by performance status, age group and nodal stage, respectively. Patients with PS 0 and stage II disease had highly significantly better QAS ($P < 0.001$) than patients with PS 1–2 and stage III disease, respectively. Younger patients had a better QAS in physical functioning ($P = 0.00002$), but not in other domains. Gender, T-stage and tumour location did not influence QAS (data not shown).

5. Discussion

Our study represented one of the largest adjuvant randomised controlled study conducted to date in CRC which included longitudinal quality of life assessment both during treatment and follow-up. Not only could difference between treatment arms be assessed, our study also provided insight into the QOL of long-term survivors of resected CRC in a longitudinal fashion. As the bolus 5-FU/LV regimen used in our study is one of the most widely used adjuvant treatment regimen in colon cancer and is likely to remain so until further confirmatory adjuvant data on combination regimens become available, our QOL data formed an unique source of information for clinicians to discuss adjuvant treatment with patients in the clinic.

In this analysis, we have shown that 12 weeks of adjuvant PVI 5-FU was associated with significant better QOL during treatment and faster time to recovery compared to bolus 5-FU/LV in patients with curatively resected stage II and III colorectal cancer. The subjective symptom scores mirrored the objective toxicity assessment reinforcing the validity that PVI 5-FU had a better toxicity profile than bolus 5-FU/LV. There was a significant difference in the deterioration of QOL scores at week 2 with bolus 5-FU/LV arm compared to PVI 5-FU arm, coinciding with the toxicity peak during the first cycle. Following week 12, global QOL recovered to baseline in the PVI 5-FU arm. This recovery was, however, delayed in the bolus 5-FU/LV because the treatment duration was 6 months. Apart from global health status, this difference between the treatment arms was also reflected in other functioning domains.

Our study has also shown that QOL score significantly improved during follow-up compared to baseline in both treatment arms. This improvement reached a plateau by end of first year of follow-up, thus indicating the adverse effect of fluorouracil-related toxicity was short-lived. Other studies have found that QOL of long-term CRC survivors are comparable to or better than that of the general population [1,3–5] and that QOL in these long-term survivors was associated with co-morbidity rather than the original diagnosis of CRC [1,3,4]. Our data added further evidence that QOL of long-term survivors receiving adjuvant 5-FU chemotherapy was good. This may be related to a positive appreciation of everyday life with the "the experience of cancer" – the so-called response shift described in patients with colon cancer [13].

In our study, females had significant worse baseline QOL compared to males, an observation also made in another study of 199 colon cancer patients [4]. There could be gender differences in both reporting QOL and impact of surgery on QOL. We have also demonstrated that elderly patients had worse baseline physical functioning than younger patients, most likely related to slower recovery from major operation and co-morbidities, consistent to the above study [4]. As the elderly were most likely to have retired, the diagnosis of cancer and subsequent surgery would have less impact on their functioning to work or perform household jobs, less interference on their family life and social activities and less financial worries compared to their younger counterpart. These were reflected in better role, social functioning and financial perception QOL scores. No consistent trend was seen to suggest rectal cancer patients had worse diarrhoea both at baseline and over the treatment period. This is probably because only 10.5% of our patients received post-operative chemoradiation. In a study of rectal cancer patients receiving pelvic radiotherapy (RT), EORTC QLQ c30 questionnaires were completed in 42 patients [14]. At the end of RT, diarrhoea, fatigue and appetite were significant worse ($P < 0.01$) compared to pre-treatment scores. However, QOL scores also returned to pre-treatment levels 4–6 weeks after radiotherapy. In another study of 329 rectal cancer patients, AP excision and presence of stoma were associated with poor QOL [15]. However, improvement in QOL over time was only evident in patients undergoing anterior resection; reversal of temporary stomas may have contributed to this effect. However, another study yielded contradictory evidence with stoma patients reporting better social functioning than did patients without stoma, with less anxiety and higher self-esteem [5].

There are limitations to our QOL assessment. Firstly, although we used a well-validated QOL instrument-EORTC QLQ c30, this may not be sensitive to the symptoms specific to CRC patients. However, when we commenced the study in 1993, the CRC module (QLQ-CR38) was not yet developed [16]. Secondly, we did not collect QOL data after patients had experienced disease relapse. This might have contributed to the lack of difference in QOL during follow-up between the treatment arms, as bolus 5-FU/LV was associated with more disease relapses. However, the institution of palliative chemotherapy or resection of metastasis could not be

controlled for in our trial population and might have highly variable impact on patients' QOL, therefore this remains an unresolved and challenging issue.

Most of the studies evaluating quality of life adjusted survival used the Q-TWIST method [17–24]. No studies have evaluated QALYs in colon cancer and only one study evaluated QALYs in rectal cancer [22] and this rectal cancer study confirmed the superiority in QOL of chemoradiation over radiation alone. We had the advantage of having longitudinal QOL. Therefore, rather than relying on toxicity, disease recurrence and survival data as used in the Q-TWIST model which does not take into account of the patients' subjective perception of QOL, we integrated the product of the group QOL mean and the survival function [11] to perform quality adjusted survival analysis. PVI 5-FU was associated with a trend towards better QAS in all functional domains and global health status compared with bolus 5-FU/LV. However, as the major differences in QOL between the two arms were in the first 6 months without any long-term toxicity and no QOL data were collected after disease relapse, QALY were probably more heavily influenced by survival rather than QOL.

With the advent of oral fluoropyrimidines, our data may have further implications. The use of capecitabine in adjuvant setting is being addressed in the X-ACT study. Compared to bolus 5-FU/LV, capecitabine was also associated with significantly reduced neutropenia, diarrhoea, stomatits, nausea and vomiting and alopecia in the adjuvant setting [25] as well as equivalent efficacy [26]. The use of oral fluoropyrimidines will certainly simplify the administration of adjuvant chemotherapy for early stage colon cancer.

In conclusions, PVI 5-FU was associated with significantly better quality of life during treatment. Due to the shorter treatment duration, PVI 5-FU arm had a faster time of QOL recovery. Significant differences in baseline QOL existed between genders, age and tumour locations. Quality adjusted survival was also in favour of the PVI 5-FU arm. In view of non-inferior efficacy compared to bolus 5-FU/LV, these data support the use of short duration infused 5-FU as adjuvant therapy for curative resected stage II and III colorectal cancer.

Conflict of interest statement

None declared.

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