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## Research paper

# The importance of stabilization as an endpoint in the treatment of metastatic colorectal carcinoma: recent quality of life studies

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**Assessment of the effectiveness of new anticancer chemotherapies in clinical trials is usually based on the degree of objective response obtained. Response is usually defined as 'complete', when there is complete disappearance of all detectable tumor, or 'partial', when there is a 50% reduction in the sum of the products of the largest perpendicular diameters of all measurable disease, with no new lesions (Advanced Colorectal Cancer Meta-analysis Project). Both clinicians, concerned with the welfare of their patients, and healthcare administrators, keen to be assured of cost-effectiveness within their restricted budgets, see such response (along with enhanced survival) as a cardinal indicator of efficacy. Response rates are a primary influence on their decision to treat, or to sanction payment for treatment, with a particular medication. There is, however, growing evidence to suggest that *stabilization* of disease is also an important endpoint in chemotherapy for carcinoma, with important benefits for the patients' quality of life (QoL). We report on recent international studies on the effects of the topoisomerase I inhibitor irinotecan (Campto®) as second-line treatment in patients with metastatic colorectal cancer. These confirm the value of stabilization, as well as response, in such patients, not only in bringing QoL benefits, but also in reducing length of hospitalization and hence costs.** 

*Key words*: Colorectal carcinoma, endpoint, quality of life, stabilization.

## Introduction

After lung cancer, colorectal carcinoma remains the second most common cancer in the UK, with some 27 000 new cases diagnosed each year in the UK and some 18 000 deaths reported annually.[1] About 5% of the population of the Western world will be affected by colorectal cancer at some point during their lives.[2]

Overall, about 50% of patients can expect to be cured by radical surgery. Adjuvant chemotherapy is also known to prolong survival for Duke's C. Some 50% of patients, however, develop metastatic disease (including approximately 25% of patients who have evidence of metastases at diagnosis) and their prognosis is poor.[3]

While there is controversy over the value and appropriateness of anticancer chemotherapy, there is increasing evidence that such therapy can extend life expectancy in patients with metastatic colorectal cancer. Scheithauer *et al.* indicated a *doubling* of survival (11 versus 5 months) with systemic 5-fluorouracil (5-FU) compared with best supportive care (BSC). Furthermore, it seems that patients can achieve a significant benefit from early rather than late chemotherapy (survival: 14 versus 9 months).[4,5]

5-FU has been the most effective first-line agent in the treatment of advanced colorectal cancer for 40 years and currently a combination of 5-FU with the biochemical modulator folinic acid (leucovorin) is considered the standard treatment for this malignancy. Trials in previously untreated patients show the median response rate to be around 30%.[6]

Patients failing on 5-FU (many of them still relatively fit) may, however, not be offered further chemotherapy. They are managed by BSC, with a correspondingly short survival time.

The introduction of the topoisomerase I inhibitor, irinotecan (Campto®), is a significant advance. It means that an active, effective second-line treatment for patients with metastatic colorectal cancer is now available.[7,8]

The response rate to irinotecan in patients with 5-FU-resistant metastatic colorectal cancer in a phase II trial was some 14%, with a further 44% of patients experiencing stabilization of the disease.[9] In other words, there is control of tumor growth in more than 50% of advanced colorectal cancer patients given this further treatment.

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In multicenter European phase II studies, median survival was some 14.5 months for responders and 12.5 months for patients with stable disease, compared with 9 months for those with progressive disease.[10]

As well as enhanced survival ('quantity of life'), the quality of life (QoL) that can be provided for these advanced colorectal carcinoma patients is clearly also important. Patients who respond or who are stabilized by chemotherapy may experience other changes—such as increased or stabilized performance status, weight gain (or stabilization) and pain control—which may also improve their QoL.[10]

Previously, however, only a few studies have tried to assess the effects of second-line chemotherapy on patients' QoL. We report here on new QoL studies in three European countries.

## French QoL and resource use study

A French prospective study on outcomes and costs[11] involved 80 patients with metastatic colorectal cancer at 21 hospitals. They were beginning second-line chemotherapy following failure of first-line palliative treatment or progression through adjuvant chemotherapy. The aim of the study was to assess the effects of stabilization of disease (as well as objective response) on QoL and resource use.

There were four main types of regimen, outlined in Table 1.

Regardless of which type of treatment they received patients were categorized into seven health states:

(i) Initial 6 weeks of treatment.
(ii) Terminal, 2 weeks before death.
(iii) Early progressive disease (EPD).
(iv) Progressive disease (PD).
(v) Objective stable disease (SD).
(vi) Clinically stable disease (CSD).
(vii) Partial response (PR).

Figure 1 shows the history of patients through the 16 week study.

QoL was evaluated through self-completed questionnaires. There were four 'generic' dimensions, derived from the McMaster Multi-Attribute Health Status (MAHS) and five dimensions 'specific' to metastatic cancer, according to the format developed by the health economics research organizations MEDTAP International and ARCOS (see Table 2)

Average scores for each health state were recorded, together with average variations per health state at weeks 8 and 16. The use of hospital resources in the treatment of disease or in treating chemotherapy complications was also assessed.

Stable disease [both objective (SD) and clinical (CSD)] was midway between partial response (PR) and progressive disease (PD and EPD) in mean QoL scores for *mobility*, *cognition*, *outlook*, *emotion* and *tiredness*.

For *self-care* and *pain* the QoL scores for SD and CSD were closer to PR than to PD. *Hair loss* and *nausea* did not discriminate between health states.

Responders and patients with stable disease had better QoL scores than before treatment. Patients with stable disease benefited greatly in enhanced *mobility*, *self-care* and *emotion scores*, and, to a lesser extent, in improved *energy* and *outlook*. In these patients, *pain* tended to stabilize at initial levels (see Figure 2).

The assessments of resource use showed that stable patients (SD and CSD) spent significantly *less time* in hospital, and *cost less* on average, than PD and EPD patients. As far as cancer-related costs were concerned, SD, CSD and PR patients incurred similar costs and were much less costly than PD and EPD patients.

**Table 1.** Treatment regimens

| Type of second-line chemotherapy | Number of patients |
|---|---|
| 5-FU+modulators (e.g. leucovorin) | 31 |
| (of which 'de Gramont'[13]) | (21) |
| 5-FU only | 9 |
| (of which protracted infusion) | (6) |
| Oxaliplatin associated with 5-FU/leucovorin | 22 |
| Irinotecan (Campto®) | 18 |
| Total | 80 |

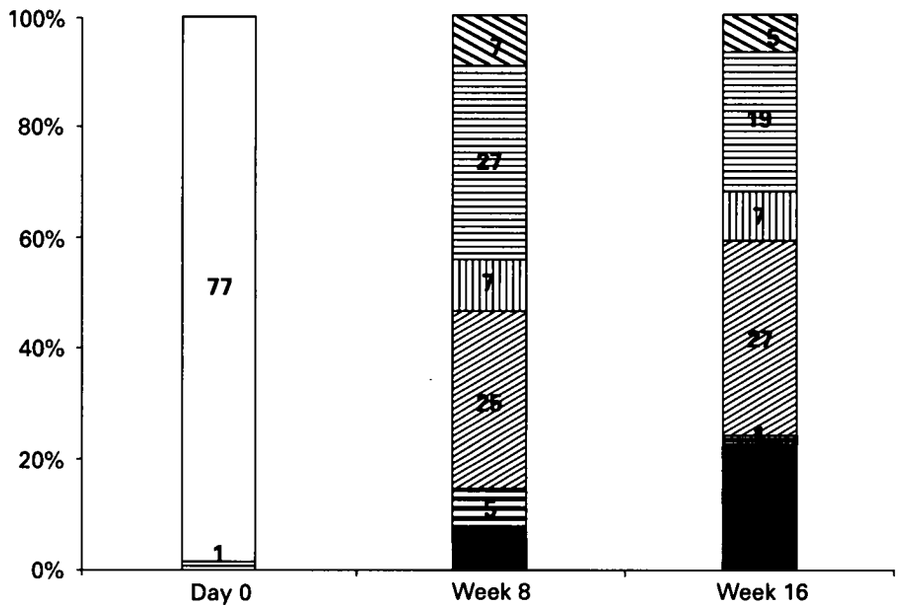


**Figure 1.** History of patients on study. ☐, initial; ▨, PR; ▤, SD; ▥, CSD; ▨, PD; ▥, EPD; ☐, terminal; ■,

**Table 2.** Self-completed questionaire: QoL dimensions

| |
|---|
| *Generic dimensions* |
| mobility |
| self-care |
| cognition |
| pain |
| *Other 'specific' dimensions* |
| alopecia |
| nausea/vomiting |
| outlook (perception of future) |
| emotion (fear/anxiety) |
| tiredness/energy |

'Progressive' (PD and EPD) patients were *hospitalized* to a far greater extent than 'stable' patients (SD and CSD), both overall and for cancer-related admissions (see Table 3).

The *incidence* of hospital admissions and their *duration* were also much reduced in stable patients compared with those with progressive disease. (Total number of days in hospital: stable disease=33 days versus progressive disease=193 days. Average number of days in hospital during any 1 month: stable disease=0.36 versus progressive disease=2.12.) (See Figures 3 and 4.)

## British utility study

'Utility' is a measure of the strength of people's preferences for being in various states of health. A major influence on their preferences is perceived QoL.

Because utilities put figures on the relative value of different health states, it makes them more useful than conventional QoL measures. Utility studies are becoming more common, although few have been carried out on cancer therapies.

A recent utility study involved 30 specialist oncology nurses (from six British hospitals) who had many years of experience in caring for oncology patients.[13]

They were asked to assess a number of different health states related to colorectal cancer and its treatment. Nurses were used as proxy for patients because it was felt that patients might be distressed by being asked to assess health states. Furthermore, some patients had deteriorated to a health state where they were unable to answer QoL questions. Nurses were considered to be a good proxy for patients' feelings, not least because of the close relationships they frequently establish.

Descriptions of 23 health states related to colorectal cancer and its treatment were drawn up. These included partial response, stable disease and progressive disease, both with and without toxicity such as hand-foot syndrome, neutropenia, diarrhoea and nausea/vomiting. A typical description is shown in Figure 5. Descriptions of Worst Possible Health and Best Possible Health were set as boundaries, with values of 0 and 100, respectively.

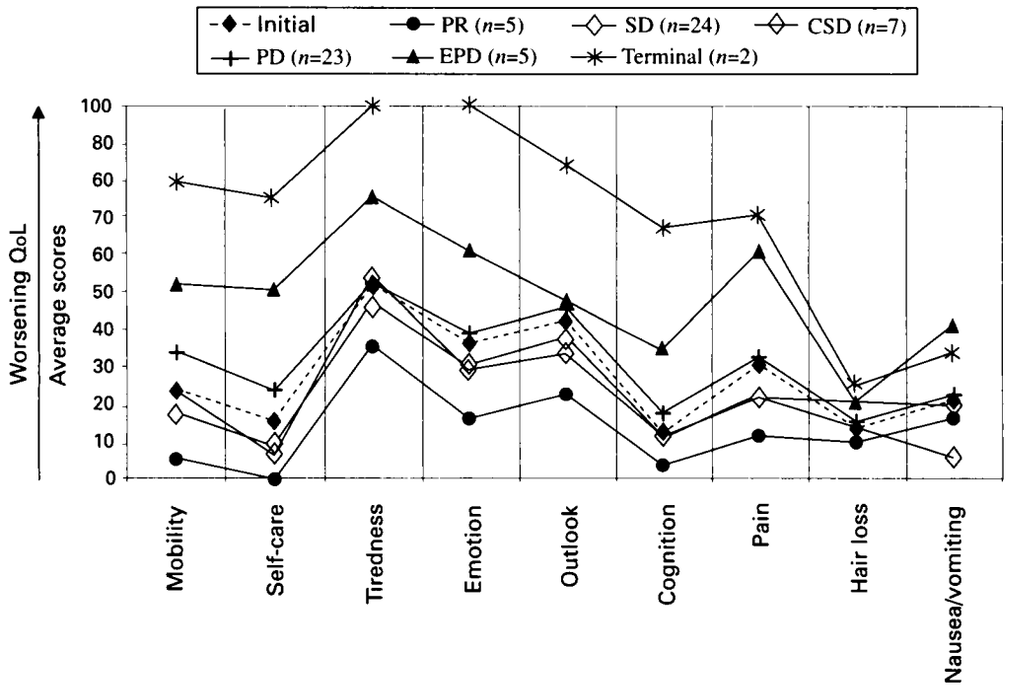


**Figure 2.** QoL profile in seven health states.

**Table 3.** Hospitalizations by health state

| Hospitalization | Responders (*n*=9) | Stable disease (SD and CSD) (*n*=33) | Progressive disease (PD and EPD) (*n*=43) |
|---|---|---|---|
| Total | 1 (11%) | 6 (18%) | 21 (49%) |
| Cancer related | 0 (0%) | 2 (6%) | 14 (33%) |
| Toxicity related | 0 (0%) | 3 (9%) | 5 (12%) |
| Metastasis resection | 1 (11%) | 1 (3%) | 0 (0%) |
| Other causes | 0 (0%) | 0 (0%) | 2 (5%) |

After familiarization ranking procedures, the nurses were asked to assess the health state descriptions using the Standard Gamble technique, the classical method for measuring preferences.[14]

Participants were presented with one description at a time and asked to make a choice between definitely being in that health state (Choice A) or gambling on either being in the Best or in the Worst Possible Health (Choice B). The levels of chance for being in Best or Worst Possible Health were then varied. The rating score for each health state was the level of chance for being in Best Possible Health which made the participants *indifferent* to which choice they made.

The median scores for the Utility (i.e. the perceived 'value' of the QoL) for the various health states in colorectal cancer (assuming no toxicity) are shown in Table 4.

The QoL of patients with stable disease was valued almost as highly as those with partial response. Patients were therefore considered to benefit strongly from chemotherapy if they achieved at least stabilization of the disease. On the other hand, it was clear that if the patient had not responded or stabilized, the nurses thought it would be better to stop the chemotherapy.

Side effects were also perceived to have a significant impact on the QoL of patients, so the major QoL gain from stabilization needs to be balanced against the QoL costs from toxicity.

In this study different toxicities were seen to impact very differently on the patient. Hand-foot syndrome or an episode of febrile neutropenia (WHO grade 3-4),

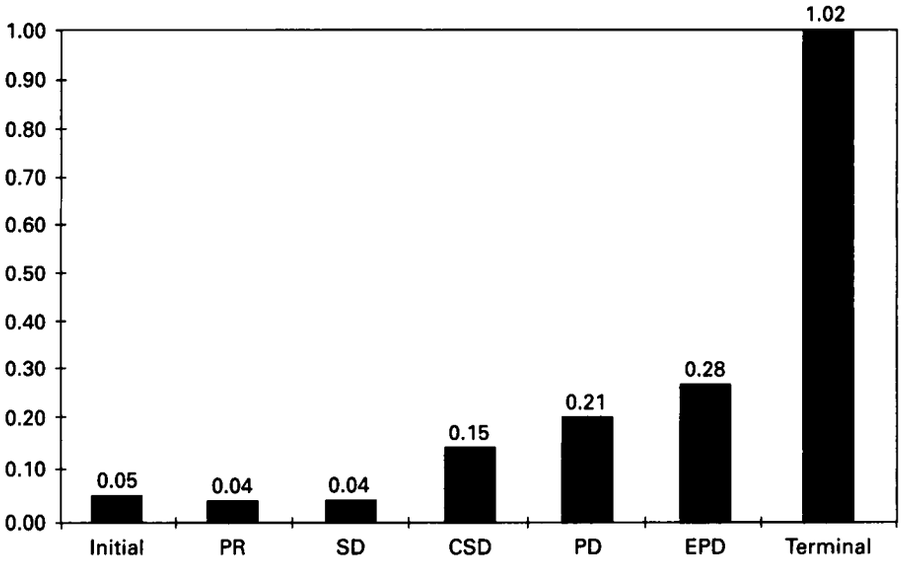


**Figure 3.** Incidence of hospital stays/health state: overall.

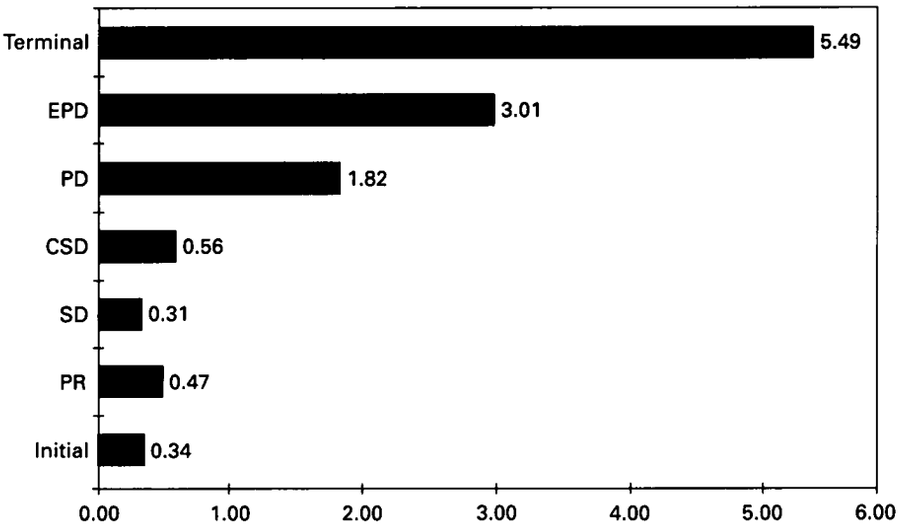


**Figure 4.** Number of hospital days/month per health state: overall.

for example, did not have a significant effect in reducing the value of the health state, 'costing' some 20-25 utility points. On the other hand, a grade 3-4 nausea/vomiting episode (costing between 55 and 62.5 points) and mucositis (costing between 57.5 and 62.5 points), were perceived as much worse. A grade 3-4 diarrhea episode came between these two extremes, costing some 32.5-50 points.

It should, however, be noted that utility scores represent only the perceived value of the patients' QoL *at a given moment in time*. Side effects are of shorter duration than the benefits of the chemotherapy: a partial response or stabilization may be sustained for several months while, for example, nausea and vomiting usually lasts only a few days. The overall QoL benefit from chemotherapy in this case probably outweighs the cost from an episode of nausea and vomiting.

Further, multidisciplinary teams treating advanced cancer will be well aware that such side effects are likely to occur. Prophylactic action (e.g. with antiemetics) and concurrent therapy will relieve symptoms in many cases.

It should also be pointed out that the latest palliative treatment for metastatic colorectal cancer, using the topoisomerase I inhibitor irinotecan, provides a 50% chance of response or stabilization for more than four months, but there is only a 19% chance of grade 3–4 nausea/vomiting and a 26% chance of grade 3–4 diarrhea.[15] This weighs even more heavily therefore in favor of palliative chemotherapy.

## Italian utility study

The preferences shown by British nurses in this utility study have been confirmed by a similar study in Italy. Italian nurses were asked to evaluate the QoL values of the various health states in the same way and their answers showed a remarkable consistency with those of their British colleagues.[11]

The ranking and magnitude of utility values for different health states were comparable. Italian nurses tended to rate progressive disease and terminal disease (TD) more severely than the British nurses, but they still regarded stabilization as providing almost as good a QoL as a partial response (see Figure 6).

**Table 4.** Utility scores for various outcomes

| Health state | Median utility value |
|---|---|
| Best Possible Health | 100 |
| Worst Possible Health | 0 |
| Partial response, no toxicity | 100 |
| Stable disease, no toxicity | 95 |
| Progressive disease | 57.5 |
| Terminal disease | 10 |

- Can walk and carry things, although *with difficulty*, needs assistance for moderate effort
- Can eat, wash, dress and go to the toilet without problem
- *Very* tired, has *many* anxieties and worries, *generally pessimistic* about the future
- *Slight* hair loss
- Has *considerable* difficulty concentrating and solving problems in daily life
- Pain *relieved* by *intermediate* analgesic (Diantalvic, Eferalgan codeine)
- No nausea, vomiting or unpleasant feeling in the mouth, 8 to 10 bowel motions/day *regardless* of treatment

**Figure 5.** A typical Health State description: stable disease+isolated diarrhea (grade 3–4).

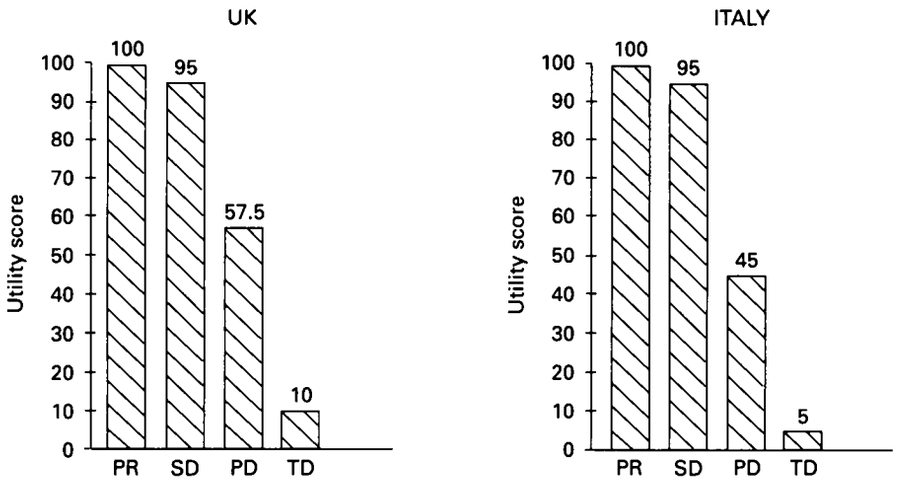


**Figure 6.** Comparison of British and Italian nurse utility studies (Best Possible Health=100; Worst Possible Health=0).

## Discussion

These studies confirm the value of stabilization, as well as response, in the second-line palliative chemotherapy of metastatic colorectal cancer.

Stabilization brings enhanced survival (12.5 months for stable patients versus 9 months for those with progressive disease)[10] and, as the studies above show, it also achieves a QoL value almost as high as that for partial response.

The studies reported here clearly demonstrate the QoL advantages of chemotherapy as compared with supportive care. The QoL benefits compensate for the negative QoL effects of toxicity in those in whom the disease is stabilized, as well as in responders. Additionally, when the side effect profile of a new drug is well documented, as with the new topoisomerase I inhibitor irinotecan, adverse effects can be minimized prophylactically and managed effectively.

Among the few prospective randomized trials which assess the patients' QoL during chemotherapy for advanced colorectal cancer is a multicenter study by the Nordic Gastrointestinal Tumor Adjuvant Therapy Group on the effects of different regimens of modulated 5-FU treatment.

This showed that while QoL improvements were usually dependent on an antitumor effect, that effect did not necessarily have to be large enough to merit an objective response. The authors reported: 'Prolonged (i.e. more than 4 months) stationary disease also appears to be favorable for the patient. This knowledge may have practical importance in the decision to recommend palliative chemotherapy'.[16]

A German team involved in trials with various regimens of modulated 5-FU in advanced gastric, pancreatic and colorectal cancers reported that objective palliative effects of treatment do not necessarily correlate with the rate of objective responses. They said that additional endpoints are called for, 'representing aspects of palliation and overall benefit of treatment'.

They added: 'Since overall survival is not influenced by the rate of tumor reduction, the obsession with measuring objective response rates alone in advanced gastrointestinal cancer has to be reconsidered. Study endpoints such as time without symptoms, toxicity of treatment, time to progression and quality of life under treatment should be emphasized in the design of clinical trials in gastrointestinal cancers'.[17]

Finally, as a review of current treatment modalities in advanced colorectal carcinoma in *Recent Results in Cancer Research* commented: 'Since all treatment strategies in advanced colorectal cancer are still palliative, Quality of Life is a more important endpoint [than response or survival] in clinical trials'.[6]

When the effectiveness of second-line therapy is being assessed, the improvements in QoL parameters for both responders *and* stabilized patients should be borne in mind, in addition to tumor response. We also suggest that future research should try to assess the psychological as well as the physiological impact of chemotherapy.

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