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Supportive care for patients with gastrointestinal cancer (Review)

Ahmed N, Ahmedzai S, Vora V, Harrison S, Paz S

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[Intervention Review]

Supportive care for patients with gastrointestinal cancer

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ABSTRACT

Background

This review is an update of a previously published update review in The Cochrane Database of Systematic Reviews (Issue 4, 2006) on this topic. No new studies have been identified from the update search and the conclusions are not altered. Supportive care has traditionally been given to optimise the comfort of patients and their ability to function, as well as to minimise the side-effects of anti-cancer treatments. However, the scope of modern comprehensive supportive care is broadening and covers not only specific palliative treatment but non-tumour specific treatment such as social, psychological and spiritual support. In oncology, best supportive care (BSC) has been used as a comparator arm of randomised controlled trials in chemotherapy. However, the BSC arm is usually not well defined and its evaluation is therefore difficult because of the heterogeneity of the definitions. A systematic review was undertaken of the evidence from all RCTs of gastrointestinal cancers (includes gastrointestinal/gastric, colorectal/colon cancer but excludes pancreatic cancer trials) which include a BSC/SC arm.

Objectives

1. To examine effectiveness/outcomes of best supportive care interventions versus cancer therapies for gastrointestinal cancer trials;
2. To determine whether trials containing best supportive care include a definition of this.

Search methods

Electronic databases, grey literature sources, citation searching and reference checking, handsearches of journals and discussion with experts were used to identify potentially eligible trials from both published and unpublished sources up to July 2009.

Selection criteria

RCTs comparing BSC/SC versus anticancer therapies in patients with gastrointestinal cancers.

Data collection and analysis

Four RCTs were found and reviewed. Because of the heterogeneity of studies, a meta-analysis was not attempted. Data were extracted from the included studies and the quality of each was assessed.

Main results

Data from four studies (483 participants) were included. Due to the heterogeneity of studies (in terms of populations studied, the interventions used, the variety of outcomes and assessments used) it was not possible to make direct comparisons between the studies.

The primary outcome in all four trials was survival, in spite of patients with advanced/metastatic gastrointestinal cancer having a poor prognosis, and the interventions being primarily palliative.

Authors' conclusions

Overall the results show that for most of the studies included in this review, certain forms of chemotherapy plus supportive care improve both survival and quality of life in patients with gastrointestinal cancer (gastric and colorectal cancers) compared to receiving supportive care alone. Trials involving BSC/SC in patients with advanced gastrointestinal cancer require careful evaluation. Oncologists and researchers alike should strive for improvements in trial design and reporting. Future trials should focus on clearer definitions of supportive care. The EORTC definition of supportive care can be used as a guide. BSC/SC trials should use standardised validated outcome measures for symptom control, quality of life, toxicity and other useful palliative measures.

PLAIN LANGUAGE SUMMARY

Supportive care for patients with gastrointestinal cancer

Certain forms of chemotherapy plus supportive care improve both survival and quality of life in patients with advanced gastrointestinal cancers compared to supportive care alone. Gastrointestinal cancer is the second most common form of cancer and is associated with a high mortality. There is some consistent evidence that patients with advanced gastrointestinal cancer benefit in both survival and quality of life by a combination of chemotherapy plus supportive care compared to receiving supportive care alone.

BACKGROUND

This review is an update of the same previously published update review in The Cochrane Database of Systematic Reviews (Issue 4, 2006) on 'Supportive care for patients with gastrointestinal cancer'. It has been estimated that of the 50 million annual deaths worldwide, about 10% are due to cancer. The International Agency for Research on Cancer estimated that in 1996 more than seven million people died of cancer. Most were cancers of the lung (1.16 million) and stomach (0.85 million) (Ahmedzai 2000; WHO 1998). Gastrointestinal tumours including colorectal cancers are one of the commonest causes of cancer deaths in Western countries. Only a small number of patients present in an early stage of disease and the treatment of advanced gastrointestinal tumours is far from satisfactory (Cascinu 1995; Cunningham 1998).

Since 1988 there has been an increasing use of the terms 'Best Supportive Care' or 'Supportive Care' as a comparative arm of randomised controlled trials (RCTs) in cancer therapy (Cullen 2001). The term was first used by the authors of the National Cancer Institute of Canada in a three-arm trial which involved a control arm comparing two chemotherapy regimens with no chemotherapy in advanced non-small cell lung cancer (Rapp 1988). In oncology research, anticancer treatment arms are typically well defined and tightly prescribed. However, the best supportive care arm is usually not well defined and therefore may be left open to local interpretation, which questions the validity of these trials. In practice the term BSC/SC implies standard non-interventional care in the same cancer services.

Oncology services are becoming increasingly standardised across Europe (Ahmedzai 2001), however, supportive care and palliative care are relatively new clinical developments which may vary significantly between countries. This lack of definition and non-uniformity of best supportive care undermines the scientific basis of Randomised Controlled Trials (RCTs). Furthermore, it is also probably unfair to best supportive care as a therapeutic option, which could be as effective for symptom palliation as the oncological intervention in a number of trials, at least in some centres and countries (Ahmedzai 2001).

There are several issues that contribute to the uncertainty regarding best supportive care which need to be addressed. What is meant by 'support'; why 'best'; what is it better than; who is supposed to give the support? In the past supportive care for cancer has tended to focus on anti-emetics, antibiotics and anti-fungals, growth factors, etc. These are indeed 'supportive' in the sense that these interventions are not designed to cure the underlying cancer, but they are mostly addressing the toxicities of anti-cancer therapies.

Ideally supportive care should be aimed at supporting the patient and, where appropriate, the patient's family and carers. The cause of the problems which face the people with cancer may not be their prime concern. What matters is whether their problems can be dealt with, so that anti-cancer therapy can be pursued as far as possible, and that palliative treatments can also be made available whenever they are needed. These are reasonable requests from cancer patients but, at least in the context of clinical trials, how can these interventions under the heading of 'supportive care' be described and defined?

To clarify what is meant by best supportive care, it is helpful to consider whether the purposes of supportive care are:

1. to give more intensive and effective anti-cancer therapy?
2. to improve quality of life for patients with cancer?

If the primary purpose of best supportive care is (1), then at least the measures which should be made available must be defined, listed in protocols. Some means should be identified to ensure that patients receive these supportive care interventions, and that they are recorded in the case report forms. Otherwise it will not be clear, for example, if the reduction in emesis associated with a chemotherapy regimen is due to a smaller inherent emetic potential of the drugs, or because some of the centres were using better anti-emetic regimens. Documentation about supportive care interventions should be done to the same high standard as the other variables collected in clinical trials e.g. Good Clinical Practice guidelines (Ahmedzai 2001).

If the aims of best supportive care include (2), then it is crucial that a broader view is taken of what comprises 'support', and, furthermore, this aim could clearly have implications for the care of cancer patients outside of clinical trials. Consequently, it is regarded as unduly narrow to think of supportive care in the context of cancer clinical trials without considering the overall picture of cancer services delivery and the provision of palliative care services.

OBJECTIVES

This was a re-visit of the literature and the original objectives were to systematically review the evidence from all RCTs of gastrointestinal and colorectal cancers (excluding pancreatic and other cancers of the biliary tract) which include a BSC/SC arm in order to:

- examine the effectiveness/outcomes of best supportive care interventions versus cancer therapies for gastrointestinal cancer trials;
- determine whether trials containing best supportive care include a definition of this.

METHODS

Criteria for considering studies for this review

Types of studies

To be considered for inclusion, clinical studies had to be RCTs of interventions for gastrointestinal cancer which have a BSC/SC arm. Trials which included both gastrointestinal and pancreatic/biliary cancer patients were included, however, data from the gastrointestinal cancer patients only was undertaken. Studies also had to include at least one of the following outcome parameters: symptom control, pain relief, or quality of life. Trials reporting data from patients with pancreatic and biliary cancers only were excluded.

Types of participants

Patients of 18 years and over who were diagnosed with and treated for cancer of the stomach, gastrointestinal/gastric, or colorectal/colon cancer in any health care setting (in the community; hospital; nursing homes or chronic care institutions; outpatients).

Types of interventions

The types of interventions included in the review were: 1) chemotherapy (any type of chemotherapy for any duration); radiotherapy; surgery; and 2) BSC/SC. The EORTC definition of supportive care was used as a 'gold standard' for the inclusion of studies. However other trials which do not meet this 'gold standard' were also included provided they met the other inclusion criteria stated. These were separated in the sub-group analysis and the results compared.

Types of outcome measures

All patient outcomes were considered and reflected the outcomes that are most important for patients. However, outcomes may be different if patients are having 'curative' treatment rather than palliation of symptoms. For patients who are terminally ill, quality of life, symptom control and pain relief are of primary concern, whilst those who are undergoing curative treatment, tumour response, improvement and adverse effects are of primary concern. We focused on the following outcomes:

- symptom control,
- pain severity and pain relief,
- quality of life,
- any reported adverse side effects,
- hospitalisation due to adverse effects,
- length of improvement,
- length of survival,
- disease progression.

Validated methods for measuring pain relief

Three general types of pain measurement scales have proven to be useful in a variety of clinical and research settings: categorical scales; visual analogue scales (VAS); and numeric scales (Osoba 1991). Data were collected for pain outcomes assessed using any of these scales.

Validated methods for measuring quality of life

The most widely used, standardised, validated methods of measuring quality of life are: the EORTC Quality of Life Questionnaire (EORTC QLQ-C30) (Aaronson 1993); the Quality-of-Life Index (QLI); the Functional Living Index-Cancer (FLIC), the Rotterdam Symptom Checklist (RSCL), and the Functional Assessment of Cancer Therapy (FACT). Quality of life measures using any of these scales and other published scales were accepted (Staquet 1998). By restricting the number of quality of life and symptom scales it is possible to make valid comparisons between the studies on subjective outcomes.

Search methods for identification of studies

The literature search aimed to identify all high quality studies of randomised controlled trials relating to supportive care for gastrointestinal cancer. Search strategies included the terms: (best) supportive care, gastrointestinal neoplasms, pancreatic neoplasms, etc. Please see Appendix 1 for MEDLINE search strategy and also Appendix 2 for additional search strategies. Studies reporting data from pancreatic cancer patients were excluded. However, mixed populations were included if separate data was available for the other types of cancers, or when the authors provide these data. No restrictions were placed in the search strategy regarding the years or languages of papers.

The following sources were searched:

Electronic databases

The following electronic databases were searched using the search terms listed above:

1. MEDLINE (OVID BIOMED 1966 to 2002 and subsequent searches ran in 2006 and July 2009)
2. EMBASE (SilverPlatter WebSPIRS 1980 to 2002 and subsequent searches ran in 2006 and July 2009)
3. CDSR (The Cochrane Database of Systematic Reviews, Issue 2, 2001 with subsequent searches ran in Issue 3, 2006 and Issue 3, 2009)
4. CCTR (The Cochrane Database of Systematic Reviews, Issue 2, 2001 with subsequent searches ran in Issue 3, 2006 and Issue 3, 2009)
5. Best Evidence (1991 to 2001)
6. DARE (The Cochrane Database of Systematic Reviews, Issue 2, 2001 with subsequent searches ran in Issue 3, 2006 and Issue 3, 2009).
7. NEED (The Cochrane Database of Systematic Reviews, Issue 2, 2001 with subsequent searches ran in Issue 3, 2006 and Issue 3, 2009)
8. HTA (The Cochrane Database of Systematic Reviews, Issue 2, 2001 with subsequent searches ran in Issue 3, 2006 and Issue 3, 2009).
9. CINAHL (1982 to 2001 with subsequent searches run in 2006 and July 2009)
10. HealthSTAR (1975 to 2001)
11. Citation Indexes (Science and Social Science 1981 to 2001)
12. CancerLIT (1966 to 2001)
13. Oncolink (1994 to 2001)
14. PsycINFO (1967 to 2001, with subsequent searches in 2006 and July 2009)

'Grey' literature sources

'Grey' literature sources (e.g., HMIC, SIGLE, Index to Theses, Dissertation Abstracts) and current research and trials registers (e.g., the National Research Register) were also searched. In addition, key Internet sites in the field were identified via a search using Copernic, a meta-search engine that allows several Internet search engines to be searched simultaneously.

Citation searching and reference checking

Citation searches of included studies were undertaken using the SCI and SSCI citation search facility, and the reference lists of relevant articles were reviewed.

Handsearching

The contents pages of key journals in the field were scanned by The Cochrane Collaboration's hand searchers in an attempt to pick up articles not already indexed on the electronic databases, and/or entered into the Cochrane Controlled Trials Register (CCTR). The following five high impact journals were handsearched:

1. Annals of Oncology (1999 to 2001);

2. British Journal of Cancer (Vol 84 No. 7 at http://www.idealibrary.com/links/toc/bjoc);
3. European Journal of Cancer (1997 to 2001);
4. Supportive Care in Cancer (2001);
5. Cancer Reviews (1998 to 2001).

Contacting experts in the field

Relevant professional and research organisations were contacted to identify any additional published or unpublished research of relevance.

Data collection and analysis

Methods used to collect data from included studies

A total of 1980 citations were identified from the initial searches. Three review authors initially screened all 1980 citations for relevance. Citations/abstracts that appeared to refer to an RCT were assessed by two review authors to identify all relevant papers. Full text copies were then requested. Trials which were identified after mutual agreement were included in the review. Each review author extracted the data separately and then compared and resolved any differences by consensus. A third review author was employed for unresolved differences. All studies which appeared initially to meet the set inclusion criteria, but on closer examination failed to, were detailed in the 'Table of Excluded Studies'. We also wrote to authors/institutions in an attempt to obtain missing information.

Methodological quality of included studies

Studies that have been published in duplicate were included only once. Abstracts were not included. The authors of relevant abstracts were contacted in order to determine if a full paper version of the study was available. Two readers, one with research review experience and the second medically qualified, read the selected articles and assessed the quality of the trials independently. Quality assessment was undertaken using the two methods described below.

Method 1

Each study was assessed using the Oxford Quality Scale with a zero to five point scale described by Jadad 1996 and colleagues and summarised as follows:

1. was the study described as randomised (1 = yes; 0 = no)?;
2. was the study described as double-blind (1 = yes; 0 = no)?;
3. was there a description of withdrawals and dropouts (1 = yes; 0 = no)?;
4. was the method of randomisation well described and appropriate (1 = yes; 0 = no)?;
5. was the method of double-blinding well described and appropriate (1 = yes; 0 = no)?;
6. deduct one point if methods for randomisation/blinding were inappropriate.

Scoring system: maximum score = 5; minimum score = 0.

Studies were excluded if they failed to meet criterion (1).

Method 2

We used previously published criteria on the quality of palliative trials (Rinck 1997), 'Criteria to assess the quality of randomised clinical trials in comprehensive palliative cancer care'.

a) Quality criteria accrual of the study population

- Are all potential cases identified?
- Are eligibility criteria relevant?
- Is patient refusal rate < 10%?

b) Homogeneity and patient characteristics

- Is health status an inclusion criterion?
- Is disease stage an inclusion criterion?
- Is type of cancer an inclusion criterion?
- Are baseline characteristics described?

c) Randomisation

- Is randomisation procedure described?
- Is randomisation procedure correct?

d) Attrition and sample size

- Is attrition <10%?
- Is the sample size >100, or is statistical power reasonable?
- Is the power analysis calculated correctly?

e) Interventions

- Is the contrast between the interventions well defined?
- Are the interventions executed according to these definitions?
- Is contamination ruled out?

f) Outcome measurement

- Are relevant outcome variables assessed?
- Are possible confounders assessed?
- Is timing of the follow-up accurate?
- Are validated outcome instruments used?

g) Presentation of results

- Is the presentation of results clear?
- Can the results be derived from the reported data?

Scoring system: score one point if criteria for each section (a) to (g) are fully applied; score 0.5 point if criteria are not fully applied; score zero if criteria are (mostly) not applied. NR = Not Reported; maximum score = 7; minimum score = 0.

Statistical considerations

All data were extracted to a standard data extraction form. Unfortunately, there were insufficient studies that used comparable outcome measures and because of the heterogeneity between the studies, meta-analysis was deemed inappropriate. A narrative synthesis was attempted.

RESULTS

Description of studies

This is an update of the review and no new studies were found beyond those already searched on the initial review and the 2006 update.

Fourteen studies were identified which appeared to fit the inclusion criteria. On closer examination only seven were found to be randomised trials. Of these seven, only four had outcomes that were considered relevant and were therefore included in the review (see 'Characteristics of included studies' table). Ten studies were excluded from this review, and the reasons for exclusion have been listed in the 'Characteristics of excluded studies' table.

All four included studies examined the impact of chemotherapy plus supportive care versus supportive care alone on patients with advanced/metastatic gastrointestinal cancer.

Chemotherapy treatments for the four studies were:

- octreotide (Cascinu 1995);
- irinotecan (Cunningham 1998);
- ELF regimen which consisted of 5-FU and leucovorin and etoposide or FLv regimen which consisted of 5-FU and leucovorin (elderly patients with a poor performance status) (Glimelius 1997); and
- combination chemotherapy consisting of 5-FU, leucovorin, and cisplatin (Scheithauer 1993).

The four studies included the following groups of patients:

- advanced gastrointestinal cancer patients (includes both stomach and colorectal cancer patients) refractory to chemotherapy (Cascinu 1995) (107 participants);
- metastatic colorectal cancer patients which had progressed within six months of treatment with fluorouracil (Cunningham 1998) (279 participants);
- advanced gastric cancer patients that were surgically non-curable (Glimelius 1997) (61 participants);
- previously untreated locally recurrent/metastatic colorectal cancer patients that were inoperable (Scheithauer 1993) (36 participants).

We did not find any studies comparing supportive care with either radiotherapy or surgery.

Overall, three studies examined the effect of chemotherapy on advanced/metastatic colorectal cancer patients (Cascinu 1995; Cunningham 1998; Scheithauer 1993) and two studies examined the impact of chemotherapy on advanced stomach/gastric cancer patients (Cascinu 1995; and Glimelius 1997 respectively).

All four studies had two-way comparisons. Two studies used the term best supportive care (Cascinu 1995; Glimelius 1997), and two studies used the term supportive care to define the comparative arm of the study (Cunningham 1998; Scheithauer 1993).

A total of 483 participants were randomised in these trials; all four studies involved participants with advanced stages of the illness. Scheithauer 1993 conducted the trial with least number of participants (n = 36), and Cunningham 1998 conducted the trial with the most number of patrticipants (n = 279).

Trials were published between 1993 (Scheithauer 1993) and 1998 (Cunningham 1998). The four studies were published in the following high quality journals; British Journal of Cancer (Cascinu 1995), the Lancet (Cunningham 1998), Annals of Oncology (Glimelius 1997), and the British Medical Journal (Scheithauer 1993). The trial duration ranged from thirteen months (Cunningham 1998) to four years (Glimelius 1997).

The four studies were conducted in the following countries: Italy (Cascinu 1995), United Kingdom (Cunningham 1998), Sweden (Glimelius 1997), and Austria (Scheithauer 1993).

It is clear that these studies are heterogeneous in terms of their aims, the dose regimens compared, the supportive care definitions, patients' ages, gender ratio, the performance status of participants recruited, and the way in which the outcomes were assessed and reported.

Main outcomes assessed

All four trials, as previously identified in the original review, reported survival as a primary outcome variable. Therefore no new studies were found which impacted on the original outcome of this systematic review.

Risk of bias in included studies

See additional Table 1 and Table 2 showing the application of the Oxford Quality Scale score (Jadad 1996) and the Rinck 1997 scale.

All four trials were described as randomised; however, the concealment of allocation was described in only one study (Cascinu 1995). Since questions two and five of the Oxford Quality scale (Jadad 1996) referred to double blinding and whether the method of double blinding was appropriate, both of these questions were deemed inappropriate for the assessment of cancer clinical trials, therefore each trial could only score a maximum of three.

- Oxford Quality Scale scores were as follows; two (Glimelius 1997); three (Cascinu 1995; Cunningham 1998; Scheithauer 1993).
- The Rinck Scores (maximum score of seven) were as follows; 4.5 (Scheithauer 1993), 5.0 (Cunningham 1998; Glimelius 1997) and 5.5 (Cascinu 1995).

Effects of interventions

No new studies were found when running the update search for this review, however, the results presented and identified in the original review are as follows:

Supportive care definitions:

See Additional Table 3.
The supportive care definitions used in these four trials were heterogeneous. Despite the differences in supportive care definitions used, there were some similarities.

All four trials reported the use of analgesics as part of the supportive care package offered. Two trials reported the use of antibiotics to control infections as part of supportive care (Cascinu 1995;

Cunningham 1998). Only one trial reported the use of psychological support as part of the supportive care available (Scheithauer 1993).

Reported Characteristics:

See Additional Table 4.
All four studies reported baseline characteristics and inclusion criteria. Only two studies reported the exclusion criteria (Cunningham 1998; Glimelius 1997). No study reported ethics committee approval for the study. All four studies reported adverse effects, and had a description of withdrawals and dropouts. The power calculation was reported in only two studies (Cascinu 1995; Cunningham 1998). Quality of life was reported in three of four studies (Cunningham 1998; Glimelius 1997; Scheithauer 1993). The EORTC QLQ-C30 questionnaire was used to assess quality of life in only two studies (Cunningham 1998; Glimelius 1997). One study assessed quality of life using Functional Living Index for Cancer (FLIC) (Scheithauer 1993). Analysis was performed according to intention-to-treat analysis in all four studies.

Length of survival

See 'Characteristics of included studies' table.

(a) Advanced colorectal and stomach cancer patients refractory to chemotherapy: octreotide therapy (patients could receive supportive care) versus BSC alone (Cascinu 1995).
Patients treated with octreotide had a significant advantage in the duration of survival. The median survival time with octreotide therapy was 20 weeks versus 11 weeks in the BSC arm (P < 0.0001). This advantage was also present considering the survival data for each tumour group. There was a statistically significant difference between the survival curves comparing patients with colorectal cancer treated with octreotide or not. Mantel Cox (log-rank, P = 0.001). There was a statistically significant difference between the two survival curves comparing patients with stomach cancer who were and were not treated with octreotide. Mantel-Cox (log-rank) (P = 0.003).

(b) Metastatic colorectal cancer patients which had progressed within six months of treatment with fluorouracil: irinotecan plus supportive versus supportive care alone (Cunningham 1998).
The overall survival was significantly better in the irinotecan group plus supportive care versus supportive care alone group, with a median one year survival of 9.2 months (36.2%) versus 6.5 months (13.8%) respectively, (P = 0.0001). The probability of survival was 2.6 times greater in the irinotecan plus supportive care group than the supportive care alone group.

(c) Metastatic colorectal cancer patients, previously untreated patients with histologically confirmed measurable colorectal cancer that was recurrent or metastatic: combination chemotherapy consisting of 5-FU, leucovorin and cisplatin plus supportive care versus no chemotherapy (supportive care alone) (Scheithauer 1993). The overall survival was significantly longer in patients treated with combination chemotherapy versus no chemotherapy (supportive care alone) (11.0 months versus five months respectively, P = 0.006).

(d) Advanced stomach cancer (surgically non-curable): chemotherapy (ELF/FLv regimen) plus BSC versus BSC alone (Glimelius 1997).
The overall survival was not significantly longer in the chemotherapy group versus BSC group (median eight months versus five months), however, after corrections for imbalances in pretreatment characteristics, chemotherapy treatment was associated with a statistically significant survival benefit (P = 0.003).

Quality of life

a) Advanced colorectal and stomach cancer patients refractory to chemotherapy: octreotide therapy (patients could receive supportive care) versus BSC alone (Cascinu 1995).
This trial did not include a quality of life measurement; however, study authors did advocate the use of such an assessment in future trials in order to determine the impact of octreotide treatment in terms of not only survival but also patients quality of life.

b) Metastatic colorectal cancer patients which had progressed within six months of treatment with fluorouracil: irinotecan plus supportive care versus supportive care alone (Cunningham 1998).
Treatment with irinotecan plus supportive care resulted in a significantly better quality of life than treatment with supportive care alone (except diarrhoea score). Time to definitive quality of life deterioration was significantly longer in the irinotecan plus supportive care group (all P values < 0.002).

c) Metastatic colorectal cancer patients, previously untreated patients with histologically confirmed measurable colorectal cancer that was recurrent or metastatic: combination chemotherapy consisting of 5-FU, leucovorin and cisplatin plus supportive care versus no chemotherapy/supportive care alone (Scheithauer 1993). There appeared to be no significant difference between the two groups in global/subgroup quality of life scores.

d) Advanced stomach cancer (surgically non-curable): chemotherapy (ELF/FLv regimen) plus BSC versus BSC alone (Glimelius 1997).
More patients in the chemotherapy (ELF/FLv regimen) plus BSC group versus BSC alone group had a significantly prolonged high quality of life for a minimum period of four months (14/31, 45% versus T2 6/30, 20% respectively, P < 0.05).

See also additional Table 5 for other outcomes assessed.

Symptom control

Symptom control was briefly described in all four trials. In Cascinu 1995 there was no subgroup analysis for symptom control. Glimelius 1997 was the only trial to describe the symptom-free period or improved symptomatology in the absence of severe toxicity. In this trial the physician considered 17 (55%) of patients treated with chemotherapy (ELF regimen consisting of 5FU, leucovorin, and etoposide plus supportive care) to have had a prolonged symptom-free period or improved symptomatology in the absence of severe toxicity.

Pain severity and pain relief

Cascinu 1995 was the only trial to describe pain-free survival, however, there was no sub-group analysis. Scheithauer 1993 did not report on pain severity and pain relief. The trials had no detailed descriptions of pain relief, or of access to pain specialists.

Reported adverse effects, withdrawals and dropouts, and hospitalisation due to adverse effects

All four trials reported adverse/side effects, as well as the withdrawals and drop outs. As expected chemotherapy regimens

resulted in more adverse effects than the supportive care alone groups. Only two trials reported hospitalisation as a result of adverse/side effects (Cascinu 1995; Cunningham 1998).

Disease progression

There was a difference in the reporting of disease progression in the four trials, with some studies reporting stable disease (Cascinu 1995; Scheithauer 1993), and some reporting on median time to disease progression (Glimelius 1997; Scheithauer 1993). In each case all differences were statistically significant and in favour of the chemotherapy plus supportive care groups for either stable disease or median time to progression (all P values < 0.005).

A comparison of the components of the EORTC definition of supportive care with those reported in the trials

Components of supportive care were characterised as being essential or important. Each trial was assessed according to whether or not a particular component of supportive care was acknowledged and reported. Most of the components of the EORTC definition of supportive care were neither acknowledged nor reported in any of the trials. The definitions of BSC/SC used by the authors were vague. The EORTC detailed definition of supportive care, and indeed the elements of supportive care were developed in 2001, and all the trials reviewed were published in 1998 or prior to this date.

DISCUSSION

The aims of this review were to examine the outcomes of surgery, radiotherapy or chemotherapy, or both, compared with supportive care in patients with gastrointestinal cancer. This updated review does not provide additional information on this treatment as no new relevant studies were included. Seven studies were found that compared chemotherapy plus supportive care with supportive care alone. However, only four of the seven RCTs of gastrointestinal cancers had outcomes that were considered relevant and were subsequently included in this review. Only two of these trials had recruited more than 100 patients (Cascinu 1995; Cunningham 1998). The heterogeneity of the studies in terms of patient population, interventions and control groups considered, meant that it was not feasible to undertake a meta-analysis. We found no trials comparing surgery or radiotherapy (or combination of surgery and radiotherapy) with supportive care. No trial conducted in a language other than English was identified. The four trials were published in high quality journals and were published between 1993 and 1998.

The results of the trial conducted by Cascinu 1995 suggests that octreotide therapy seems to confer a survival benefit in advanced gastrointestinal cancer patients (advanced stomach, gastric and colorectal cancer patients) refractory to chemotherapy. However, the authors of this study suggest the need to conduct further studies to confirm these results. In addition to this, since quality of life assessment was not included in this study, the authors have suggested that future studies should aim to determine the impact of octreotide treatment in terms of not only survival but also patients' quality of life. This was the only study to describe the concealment of allocation in detail.

The trial conducted by Cunningham 1998 recommends the use of irinotecan as the standard second line therapy in metastatic colorectal cancer for whom fluorouracil has failed as a new reference for forthcoming trials. Patients treated with irinotecan plus supportive care had a longer survival, fewer tumour-related symptoms and better quality of life than patients treated with supportive care alone.

The trial conducted by Glimelius 1997 suggests chemotherapy (ELF/FLv regimen) plus best supportive care enhances both the length and quality of life in advanced gastric cancer patients. However, the authors do not advocate the routine use of this treatment as the number of patients who benefit from it is still rather limited, and therefore recommend that it should be considered for a selective group of patients.

The trial conducted by Scheithauer 1993 suggests that combination chemotherapy (5-FU, leucovorin, and cisplatin) plus supportive care enhances both survival and quality of life in symptomatic patients with metastatic colorectal cancer. As this study had the smallest number of patients (n = 36), the results should be interpreted with caution.

Overall the results show that for most of the trials included in this review, certain forms of chemotherapy plus supportive care improve both survival, quality of life and the median time to disease progression in patients with advanced gastrointestinal cancers (stomach, gastric and colorectal cancers). The benefits of chemotherapy must however be weighed against treatment toxicity and the effect on quality of life, yet most of these trials had survival as a primary outcome measure, with both toxicity and quality of life as outcomes of secondary importance. Toxicity was well documented in all four trials, as were adverse effects of treatment and withdrawals and dropouts. Apart from the use of analgesics in the supportive care arm for pain relief in the four studies, there was no detailed description of pain severity and pain relief in two trials (Cascinu 1995 and Scheithauer 1993). Furthermore, there did not seem to be much emphasis on symptom control in the four studies which was only briefly described.

The EORTC QLQ-C30 questionnaire is the world's leading cancer quality of life questionnaire (Garratt 2002). It was used in only two of the four trials (Cunningham 1998; Glimelius 1997) to assess the quality of life. One trial used a modified version of the FLIC to assess quality of life (Scheithauer 1993), and one trial did not include a quality of life assessment (Cascinu 1995). The variety of assessments used in the four studies over varying periods makes it extremely difficult to make any direct comparisons.

Older patients over the age of 75 years were underrepresented in all four of the trials, all imposed an upper age limit for recruitment of subjects, yet colorectal cancer predominantly affects older people and over half of the deaths occur in people over the age of 75 (Silverberg 1990). However, such insidious ageism has been challenged by policy directives aimed at providing care 'regardless of age, on the basis of clinical need alone' (Department of Health 2001).

The overall quality of the studies as described by the Jadad and Rinck scales was good. The Oxford Quality scale is more appropriate to conventional RCTs of medical interventions, while the Rinck criteria are more detailed and focus on the broader aspects of trials in comprehensive palliative cancer care. All four trials had a good description of baseline characteristics, inclusion criteria, adverse/side effects, description of withdrawals and dropouts and

analysis was performed according to intention to treat. There were, however, some short-
comings with regards to fulfilling robust methodology, e.g. the detailed description of the method of randomization was poorly described in at least three of four studies (Cunningham 1998, Glimelius 1997; Scheithauer 1993). We recommend that future trials are designed and reported in accordance with the Consolidated Standards of Reporting Trials statement (CONSORT statement). This statement was developed in the mid 1990s to improve the quality of reporting of RCTs, and comprises a checklist and flow diagram for reporting an RCT. The CONSORT statement was revised in May 2000 (Moher 2001). The revised CONSORT statement includes a 22-item checklist and a flow diagram, and its aim is to help researchers improve the quality of results of simple two-group parallel RCTs covering all aspects from introduction, methods, results to discussion, with the ultimate aim of improving trial design and reporting.

Definition of supportive care in cancer

A coordinated European activity funded by the European Community and facilitated by the European Organization for Research and Treatment of Cancer (EORTC) Pain & Symptom Control Task Force, has led to the agreement of the following definition for supportive care in cancer treatment:

"Supportive care for cancer patients is the multi professional attention to the individual's overall physical, psychosocial, spiritual and cultural needs, and should be available at all stages of the illness, for patients of all ages, and regardless of the current intention of any anti-cancer treatment" (Ahmedzai 2001).

The philosophy of seeing the patient as a whole person is an acknowledgement that the effects of disease in any part of the individual's being will impact on all other areas of the self. Therefore, to offer effective supportive care the multi-professional team must assess the person holistically, and manage care in a way which allows for the inter-connectedness of the problems to be acknowledged, with team members liaising to provide care which optimises quality of life.

Physical care focuses on the impact of the primary, and often secondary, disease on the patient's activities of daily living. Levels of pain and other distressing symptoms are assessed, with a multidisciplinary care plan designed to offer combinations of pharmacological and non-pharmacological management, alongside information and explanation.

Psychosocial care focuses on understanding the emotional state of the patient, and what impact the illness has made on their functioning as a person within the family or other relationship. By necessity, a thorough assessment of this care involves all those affected by the person's illness, since roles, responsibilities, relationships and financial matters may act as triggers to intensify and exacerbate other symptomatology.

Spiritual care relates to understanding personal belief systems, including religion, which may support or distress the patient and those close to him/her through the disease process. These are often deeply personal areas for patients and have proved difficult to assess. However, an understanding of the spiritual being of a person can enable discussion and therapeutic work, together with the presence and practice of a chaplain (or faith leader). These aspects of supportive care are particularly relevant in palliative care and bereavement counseling (Wright 2004).

The assessment of cultural needs by the multidisciplinary team should ensure that care and support does not deny the patient any aspect of their regular cultural life. Cultural needs range from the provision of a suitable diet, to the intervention of an interpreter for those who cannot communicate freely in the team's language, and to the planning of cultural aspects of death, dying and funeral procedures which will be of importance to both the patient and family (Osoba 1991).

The EORTC definition is one of the first rigorous consensual attempts to encapsulate this difficult concept, and no doubt the definition will need to be updated as the subject develops and countries become more familiar and experienced with its implications. The EORTC definition of supportive care is not the same as usual care. The starting assumption is that supportive care is better than usual care. Furthermore, it is not suggested that supportive care should not be available to other treatment groups. In fact it is ethical to ensure that supportive care should be available to all other treatment groups, and active intervention to specific groups.

As well as the new definition for supportive care, the coordinated activity of the EORTC has identified several key elements and characteristics that are regarded as essential or important for implementation, particularly within the context of clinical trials. These are summarised in Appendices A and B, respectively of the report by Ahmedzai 2001.

All four trials had a description of supportive care; however, the descriptions were often vague and heterogenous, thus making direct comparisons almost impossible. In addition, most of the components of the EORTC definition of supportive care were not discussed in any of the trials. Although supportive care issues have not been considered in detail previously, any future studies addressing supportive care issues should use the EORTC definition of supportive care as a checklist thus standardizing the use of supportive care across all studies, and authors need to document the components of supportive care in more detail. The EORTC definition of supportive care should be used as a guide by those designing trials with supportive care, as some of the elements described may not be applicable to clinical trials. The EORTC definition will no doubt need to be updated as the subject develops and countries around the world become more familiar with its implications. It must however be stressed that, because the EORTC definition of supportive care was developed in 2001, it would be unrealistic and unfair to expect all of the identified trials which were conducted prior to this date to be without some methodological shortcomings with regards to both defining and reporting of supportive care trials. The use of the term 'best supportive care' which seems to imply that it is better than usual care when there is no evidence of this, should be replaced with just supportive care.

Gastrointestinal cancers are collectively the most common malignancies in the world with colorectal cancer accounting for most of these malignancies (Ahlgren 2001). Patients with advanced gastrointestinal cancers (particularly inoperable gastrointestinal cancer) are reported to have a poor prognosis, with life prolonging options being somewhat limited. A major aim in this group of patients should be symptom control and maintaining or improving their quality of life. All four trials reported survival as a primary

outcome variable. As these patients were in advanced stages of the illness, and in the context of palliative treatment, survival may be less of importance than the measurement of symptom control and quality of life. Therefore future trials should focus on these issues in addition to survival.

In summary, there is some consistent evidence that patients with advanced gastrointestinal cancer benefit in both survival and quality of life by a combination of chemotherapy plus supportive care compared to receiving supportive care alone.

AUTHORS' CONCLUSIONS

Implications for practice

Since the last version of this review no new studies were found and therefore the conclusions remain the same. Patients with advanced gastrointestinal cancer may benefit in both survival and quality of life by a combination of chemotherapy and supportive care. In addition, this work could be used to evaluate the usefulness of the EORTC definition of supportive care, and may have important consequences for the organisation of cancer services as a whole.

Implications for research

Since the last version of this review no new studies were found and therefore the conclusions remain the same. Further studies are still needed to clarify the effect of chemotherapy plus supportive care versus supportive care alone in gastrointestinal cancer patients using standardized validated instruments that examine symptom control, quality of life, toxicity, pain severity and pain relief in addition to survival and other palliative measures both prior to and after treatment completion. Furthermore, future studies should not impose upper age limits at trial entry. As this does not reflect the age distribution of the disease. Until this is achieved it is extremely difficult to make any direct comparisons between the studies. The challenge for the future is to strive for major improvements in trial design and reporting of results.

In summary, we recommend that the evidence base for this area could be further improved by the following measures:

1. better ways of appraising quality of supportive care trials;
2. improved criteria for including supportive care interventions into cancer RCTs, such as those put forward by the EORTC;
3. more large studies using standardised quality of life scales such as the EORTC QLQ-C30.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cascinu 1995

Methods	RCT: To assess the antitumour effect of octreotide vs. BSC in patients with advanced GI cancer refractory to chemotherapy Duration: Patients in both arms followed until death Jan 1990 to Dec 1992 (study recruitment period) Patients in both arms could receive supportive care. Journal: British Journal of Cancer 1995.
Participants	Participants: Advanced GI cancer patients refractory to chemotherapy Primary tumours were: stomach (n = 29) pancreas (n = 32) colon-rectum (n = 46)

Cascinu 1995 *(Continued)*

	Median Age (years and range): Octreotide: 68 (39 to 71) Controls (BSC): 66 (44 to 72) Gender: Male/Female ratio Octreotide: 35/20 Controls (BSC): 30/22. Performance Status: ECOG PS 0-2.
Interventions	Total n = 107 T1: Octreotide (n = 55) (200 micrograms three times/day for five days a week (primary tumours were stomach (15), pancreas (16) and colon-rectum (24) versus T2: Controls (BSC) (n = 52) (primary tumours were stomach (14), pancreas (16) and colon-rectum (22)
Outcomes	Survival length (primary outcome variable). Outcome variable of secondary importance was response rate. Duration of survival : T1: Significant advantage in duration of survival, median survival time T1: 20 weeks versus T2: 11 weeks (P < 0.0001) This advantage was also present considering the survival data for each tumour group Subgroup analysis: Stomach: survival curves comparing patients with stomach cancer treated with T1 (n = 15) or not (n = 14). There was a statistical difference between 2 curves: Mantel-Cox (log-rank), P = 0.003 Colon rectum Survival curves comparing patients with colorectal cancer treated with T1 (n = 24) or not (n = 22). There was a statistical difference between the two arms. Mantel-Cox (log-rank), P = 0.001. This trial had no specific quality of life data.
Notes	Authors conclusions: Octreotide therapy: seems to confer a survival benefit in advanced GI cancer patients refractory to chemotherapy. Although results are encouraging authors think that additional studies will be needed to confirm these results and to clarify other questions about dose and schedule of octreotide and the impact of octreotide treatment in terms of not only survival but also patients quality of life

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Cunningham 1998

Methods	RCT: To compare irinotecan with supportive care alone for survival, QoL and other clinical variables in patients with metastatic colorectal cancer in whom fluorouracil had failed Duration: Patients followed until death or for at least one year, beyond one year only date of death was traced. Median follow-up 13 months Patients in both arms received SC Journal: The Lancet 1998

Cunningham 1998 *(Continued)*

Participants	Participants: metastatic colorectal cancer patients which had progressed within six months of treatment with fluorouracil Median Age (years and range): Irinotecan + SC: 59 (22-75) SC alone: 62 (34-75) Gender: Male/Female ratio Irinotecan + SC: 129/60 SC alone: 52/38. Performance status: WHO PS 0-2.
Interventions	Total N = 279 T1: Irinotecan + SC (n = 189) 300 to 350mg/m2 irinotecan every three weeks with supportive care versus T2: Supportive care alone (n = 90) Ratio: 2:1
Outcomes	Overall survival (primary endpoint). Secondary objectives were impact of treatment on performance status, bodyweight, tumour-related symptoms and QOL. T1: Overall survival was significantly better (P = 0.0001), with 1 year survival: T1: 36.2% (median survival 9.2 months) versus T2: 13.8% (median survival 6.5 months). The probability of survival 2.6 times greater in T1. The survival benefit, adjusted for prognostic factors in a multivariate analysis, remained significant (P = 0.001). T1: Survival without performance status deterioration (P = 0.0001), without weight loss of more than 5% (P = 0.018) and pain-free survival (P = 0.003) were significantly better. Comparison of quality of life data gave the following differences for functional scale physical T1 62 versus T2 41 P < 0.001. Role T1 54 versus T2 36 P = 0.002 Cognitive T1 78 versus T2 68 P = 0.006 Social T1 59 versus T2 47 P = 0.006 Symptoms Fatigue T1 51 versus T2 61 P = 0.006 Pain T1 40 versus T2 53 P = 0.001 Dyspnoea T1 30 versus T2 39 P = 0.03 Appetite loss T1 36 versus T2 55 P < 0.001 Constipation T1 27 versus T2 40 P = 0.004 Diarrhoea T1 32 versus T2 18 P < 0.001 Time to definitive QoL deterioration was significantly longer in T1, whichever the chosen threshold for deterioration (all P values < 0.002)
Notes	Authors conclusions: Despite the side effects of treatment, patients who have metastatic colorectal cancer, and for whom fluorouracil has failed, have a longer survival, fewer tumour-related symptoms, and better QoL when treated with irinotecan than with SC alone. Irinotecan can therefore be recommended as the standard second line therapy in colorectal cancer and as a new reference for forthcoming trials

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Glimelius 1997

Methods	RCT: To estimate any gain in quantity and QoL produced by chemotherapy in advanced gastric cancer patients Duration: The study was performed in two phases-a pilot phase between January 1991 and May 1992 at one hospital followed by a multicentre phase between June 1992 and Feb 1995 Patients in both arms received SC

Glimelius 1997 *(Continued)*

	Journal: Annals of Oncology 1997
Participants	Participants: advanced gastric cancer (surgically non-curable) Median Age (years and range): Chemotherapy group + BSC: 64 (45 to 75) BSC group: 63 (40 to 74) Gender: Male/Female ratio Chemotherapy group: 23/8 BSC group: 22/8. Performance status: KPS < 50.
Interventions	Total N = 61 T1: Chemotherapy (n = 31) (ELF regimen, consisting of 5-fluorouracil (500 mg/2) leucovorin (350 mg/m2) and etoposide (120 mg/m2), given daily on three consecutive days and repeated every third week), or in older patients with poor performance, a 5-fluorouracil (500 mg/m2)/leucovorin regimen (60 mg/m2) (FLv) was given on 2 consecutive days every second week + BSC versus T2: BSC (n = 30) (chemotherapy was allowed if supportive measures did not result in palliation)
Outcomes	Overall survival, changes in QOL, objective responses, toxicity T1: Overall survival was longer (median eight versus T2: five months) difference not statistically significant (P = 0.12) After corrections for imbalances in pretreatment characteristics, chemotherapy treatment was, however associated with a survival benefit (P = 0.003) T1: More patients (45% 14/31) had an improved or prolonged high QoL for a minimum period of four months versus T2: (20% 6/30 P < 0.05). A similar difference was seen in the treating physician's evaluation of whether the patient was subjectively improved or continued to do well for at least four months (17/31 55% versus 6/30, 20%, P < 0.01). Quality of life at randomisation (R) and after the first two evaluations (1, 2) after two and four months respectively, in the chemotherapy and the best supportive care groups. Pain T1 at (R) 33b, at (1) 24 at (2) 23 T2 at (R) 18, at (1) 18 at (2) 18 Nausea/vomiting T1 at (R) 22b, at (1) 18 at (2) 14 T2 at (R) 9, at (1) 32 at (2) 13 b refers to a statistically significant difference (P < 0.05) between T1 and T2 groups respectively
Notes	Authors conclusions: Chemotherapy can add to both the quantity and QoL in advanced gastric cancer. The number of patients who benefit from treatment is, however still rather limited. The authors do not advocate the routine use of this treatment in the light of yet limited effects and the costs, but rather consider it to selected patients after realistic and adequate information

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Scheithauer 1993

Methods	RCT: To compare the length of survival and QoL in previously untreated patients with histologically confirmed, measurable colorectal cancer that was recurrent/metastatic Duration: between April 1988 and September 1989 40 patients accrued to the study Patients in both arms received SC

Scheithauer 1993 *(Continued)*

	Journal: British Medical Journal 1993
Participants	Participants: 40 previously untreated patients with histologically confirmed, measurable colorectal cancer (inoperable adenocarcinoma of the colon/rectum) that was locally recurrent or metastatic. Life expectancy over two months Median Age (years and range): combination chemotherapy group + SC: 63 (28 to 75) No chemotherapy (BSC) group: 69 (45 to 75). All patients: 66 (28 to 75) Gender: Male/Female ratio Combination chemotherapy group: 10/14 No chemotherapy (BSC) group: 7/5 All patients 17/19 Performance status: ECOG PS of less than or equal to 3.
Interventions	Total N = 36 T1: Combination chemotherapy (5-fluorouracil, leucovorin and cisplatin) + SC (n = 24). Chemotherapy consisted of four week cycles of intravenous leucovorin (200 mg/m2/day) followed by 5-FU (550 mg/m2/day) and cisplatin (20 mg/m2/day), each drug being given on the first four days of the cycle. versus T2: No Chemotherapy (SC) (n = 12) All patients (n = 36).
Outcomes	Length of survival and QOL score with an optimized functional living index-cancer scale (FLIC) T1: Overall survival was significantly longer T1: 11.0 months versus T2: 5.0 months; (P = 0.006). QoL: T1 versus T2: There was no significant difference between the two groups in global/subgroup QoL scores. In patients with abnormal scores before treatment, QoL seemed better in the chemotherapy arm. Quality of life in patients with metastatic colorectal cancer by treatment group. Overall response rate: T1 12/18 (67%) T2 5/8 (62%). Median (range) duration of response (months) T1 7 (4 to 18) T2 6 (4 to 9).
Notes	Authors conclusions: Chemotherapy regimen was an effective form of palliative treatment. Data indicate that chemotherapy with 5-FU, leucovorin, and cisplatin improves QoL in symptomatic patients with metastatic colorectal cancer and prolongs survival, although the small numbers of patients reduces the strength of the results, they support previous indirect evidence of a beneficial effect of chemotherapy in this disease

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

GI: Gastrointestinal
BSC: Best supportive care
SC: Supportive Care
ECOG: Eastern Cooperative Oncology Group
KPS: Karnofsky Performance Status
WHOI: World Health Organisation
PS - Performance status
QoL - Quality of life
RCT: Randomised Controlled Trial
5-FU: 5 Fluorouracil

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Barni 1995	RCT but didn't have crucial outcomes mentioned
Beretta 1994	Meeting abstract only-authors contacted
Blijham 1998	Meeting abstract only-authors contacted
Cunningham 1999	RCT however was a double publication- no supportive care definition Included Cunningham 1998 (RCT) in Cochrane review
Delfino 1993	Meeting abstract only - authors contacted
Glimelius 1994	Letter to editor
Glimelius 1995	Cost study (RCT) no good QoL measure
Petrioli 1995	Short communication. No 'Best Supportive Care' arm
Pyrhonen 1995	RCT but no suitable outcome markers
Wilke 1999	Review based on two RCTs

ADDITIONAL TABLES

Table 1. Jadad Scores - methodological quality

Author	Cascinu 1995	Cunningham 1998	Glimelius 1997	Scheithauer 1993
Quality assessment				
Described as randomised? Y / N	1	1	1	1
Described as double blind? Y/ N	0	0	0	0
Withdrawals and dropouts described Y/N	1	1	1	1
Appropriate randomisation method? Y / N	1	1	0	1
Appropriate method of blinding?	0	0	0	0
TOTAL SCORE	3	3	2	3

Table 2. Rinck Scores: methodological quality

Author	Cascinu 1995	Cunningham 1998	Glimelius 1997	Scheithauer 1993

Table 2. Rinck Scores: methodological quality *(Continued)*

Accrual	1	1	1	0.5
Homegeity	1	1	1	1
Randomisation	1	0.5	0.5	1
Attrition	0.5	0.5	0.5	0
Intervention	0.5	0.5	0.5	0.5
Outcome Assessment	0.5	0.5	0.5	0.5
Results	1	1	1	1
Total Score	5.5	5.0	5.0	4.5

Table 3. Definition of supportive care

Author	Definition
Cascinu 1995	Patients in both arms could receive supportive care such as haemotransfusions for anaemic state; antibiotics to control infections; analgesics, including non-steroidal anti-inflammatory drugs and opioids; corticosteroids; and vitamin supplements. Also patients could be treated with radiation therapy for painful osseous metastases and pelvic recurrences. In case of jaundice due to an obstruction of biliary tree a percutaneous transhepatic biliary drainage could be placed.
Cunningham 1998	In supportive care alone group, patients were given best supportive care and were seen every three weeks. Supportive care was defined as the best care available judged by attending physician, according to institutional standards for each centre. Supportive care included antibiotics, analgesics, transfusions, corticosteroids, or any other symptomatic therapy (except irinotecan or other topoisomerase I inhibitor), and/or assistance of a psychotherapist. Localised radiation therapy to alleviate symptoms such as pain was allowed provided that total dose delivered was in palliative range according to institutional standards. In irinotecan group patients were given best supportive care and irinotecan. Analysis of best supportive care Supportive care and concomitant medications were reported at each visit (every three weeks in both groups). They were classified using the WHO dictionary, and further sub-classification was done using the WHO code for anatomical therapeutic class (ATC). With these classifications, analgesics were divided into opioids or non-opioids and analysed in three week blocks.
Glimelius 1997	The principles of best supportive care, given in both randomization groups have been presented before. Best supportive care was given in both groups with the same high intensity and included psychosocial support and attempts to relieve any symptoms (analgesics, antiemetic drugs, nutritional support, corticosteroids, palliative radiotherapy, surgery and so on). These principles have been outlined in a regional care programme.
Scheithauer 1993	Supportive care consisted of analgesics, nutritional support, blood transfusions to correct severe anaemia, and psychological support. Patients were randomly allocated to receive supportive care and chemotherapy (arm A) or supportive care only (arm B).

Table 4. Table of reported characteristics

Characteristics	Cascinu 95	Cunningham 98	Glimelius 97	Scheithauer 93
Country/Location of first author	Italy	UK	Sweden	Austria
Baseline characteristics	Reported	Reported	Reported	Reported
Inclusion criteria	Reported	Reported	Reported	Reported
Exclusion criteria	Not reported	Reported	Reported	Not reported
Ethics committee approval stated	Not reported	Not reported	Not reported	Not reported
Adverse effects/side effects	Reported	Reported	Reported	Reported
Description of withdrawals and dropouts	Reported	Reported	Reported	Reported
Power calculation	Reported	Reported	Not reported	Not reported
Validation of instruments	Not included a QOL assessment in this trial.	QOLwas assessed with EORTC QLQ-C30 questionnaire (including five function scales, one global health status scale, and nine symptom scales), which was filled in at baseline, 3 and 6 weeks and then every 6 weeks.	QOL assessments were performed using EORTC-QLQ C30 version 1.0.	QOL was assessed at entry and every 2 months with the Functional Living Index for Cancer (FLIC-authors used several refinements to FLIC scale).
Analysis	Analysis was performed according to intention to treat	Analysis was performed according to intention to treat	Analysis was performed according to intention to treat	Analysis was performed according to intention to treat

Table 5. Other outcomes assessed

Author	Cascinu 1995	Cunningham 1998	Glimelius 1997	Scheithauer 1993
Symptom control	Every two weeks patients of both arms were looked after in the same setting by the same physician and nursing staff in order to record both side effects of treatment with octreotide and possible complications related to neoplastic disease. No further sub group analysis	Localised radiation therapy to alleviate symptoms such as pain was allowed provided that the total dose delivered was in the palliative range according to institutional standards	T1: Treating physician considered 17 (55%) patients to have had either a prolonged symptom-free period or improved symptomatology in the absence of severe toxicity. T2: 6(20%, P < 0.01)	Chemotherapy Group: 2 patients had to have the dose reduced by 25% because of grade 3 haematological and gastrointestinal side effects
Pain severity and pain relief	No sub group analysis. Only five patients suffered from pain at injection sites, but it did not determine the refusal of treat-	T1: Pain free survival in patients without pain was significantly longer versus T2: (P = 0.003), despite a higher proportion of patients	T1 versus T2: The average scores on most scale items and global health status did not differ between two groups at ran-	Not reported

Table 5. Other outcomes assessed *(Continued)*

	ment or reduce their compliance in taking the drug octreotide	on opioids in the supportive care group. Worst score during study for EORTC QLQ C30 pain scale mean (SE) 39.98 (2.39) versus 53.42 (3.27), P = 0.001	domistaion although there were more problems with pain and nausea/vomiting in chemotherapy group	
Any reported adverse effects	No sub group analysis. T1: No severe toxicity recorded requiring discontinuation of octreotide. 20 patients had asymptomatic hyperglycaemia, ten patients mild steatorrhoea, three patients had abdominal cramps-disappeared spontaneously after few days of continued therapy	T1: Significantly more patients experienced severe events, especially neutropenia, nausea, vomiting and diarrhoea. T2: High incidence of severe adverse events (drug related or not), especially pain and asthenia. T1: 2(1.1%) of 183 patients died of drug-related causes although in one, the association with adverse events (diarrhoea and/or febrile neutropenia) has not been clearly established	FLv treatment: toxicity was low. ELF treatment: toxicity was higher with grade 3/4 toxicities (except alopecia in five (22%) patients.ELF treated patients: had more or less total alopecia. No toxic deaths reported. One patient alive in each group at end of follow-up	T1: Toxicity was common, symptoms were generally mild-moderate. No patient stopped chemotherapy due to side effects. T2: mild nausea, diarrhoea, and infection were indicated by 2, 3, and 1 patient respectively. No other toxicities were recorded
Hospitalisation due to adverse effects	No patients in either arm developed infections requiring hospitalisation	T1: Admission for adverse events occurred in T1: 136 (72%) of patients (cumulative median: 15 days, range one to 168 days) versus T2: 57 (63%) of patients (cumulative median 11 days, range two to 87 days)	Not Reported	Not Reported
Withdrawals and dropouts	T1: four gastric cancer patients received octreotide for only six weeks, due to severe impairment of general conditions owing to rapid disease progression and died only after two weeks.	T1: n = 189 (six did not receive study medication, five lost to follow up, 123 died, 61 alive). T2: n = 90 (five patients lost to follow-up, 71 died, 14 alive)	Two patients in each group did not complete the questionnaire at randomisation due to rapidly progressing disease. Number of patients replying to questionnaire declined during follow-up, decline was more rapid in T2 (reasons for not replying to a questionnaire after two and four months were usually either death or that patient was terminally ill). After first interview, one patient in T2 refused further interviews	Forty patients were accrued to study. Two patients in each treatment arm refused to accept the treatment assigned or participate in the study, or both (thus 36 patients were eligible for analysis of response and toxicity. Thirty three of 36 patients in study had died at the end of study period. T1: 21 (87%) versus T2 : 12. The minimum follow-up of survivors was 28 months
Disease progression	Stable Disease: T1: 25 (seven stomach, seven pancreas, 11 colon-rectum) (45%) patients showed stable disease versus only T2: eight (three stomach, two pancreas, three colon rectum) (15%), (P < 0.001)	Patients had proven metastatic colorectal cancer which had progressed within six months of treatment with 5FU. No further information on disease progression during or after the trial	T1: The median time to disease progression was six (zero to20+) months versus T2: 2 (zero to 14) months (P < 0.01). The median time to objective disease progression (or deaths in patients not objectively evaluated was T1:six (zero to20+)	T1: Of 24 patients randomised eight partially responded, the median duration of response was T1:35 (16 to 56) weeks. Nine patients (38%) had stable disease, seven (29%) had progressive disease versus T2: three (25%) of 12 patients were classified as having

Table 5. Other outcomes assessed *(Continued)*

	months vs. T2: two (zero to 13) months (P = 0.03)	stable disease, nine (75%) as having progressive disease. Median time to progression: T1: 6.0 (12 to 14) months, versus T2: 2.3 (1.5 to 8.0) months, statistically significant difference (P = 0.0008)

APPENDICES

Appendix 1. MEDLINE search strategy

1. ((best adj3 support$) or (optim$ adj3 support$) or (support$ adj3 care$) or (support$ adj3 caring) or (supportive adj3 treatment$)).mp. [mp=title, subject heading word, abstract, instrumentation]
2. exp Gastrointestinal Neoplasms/
3. exp Pancreatic Neoplasms/
4. ((gastrointestinal or gastro-intestinal or esophageal or oesophageal or pancrea$ or gastric or stomach or intestin$ or cecal or appendiceal or colorectal or colonic or sigmoid or rectal or anus or "anal gland") and (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or malignan$ or metastas$)).mp. [mp=title, subject heading word, abstract, instrumentation]

The following filter was used to identify RCTs in Medline 1966 to July 2006
1. ((best or optim$) adj2 support$ adj2 (care or treatment$)).tw.
2. supportive care.tw.
3. or/1-2
4. exp gastrointestinal neoplasms/
5. pancreatic neoplasms/
6. ((gastrointestin$ or gastro-intestin$ or gastric or colon$ or colorect$ or pancreas$) adj3 (neoplasm$ or cancer$ or tumour$ or tumor$ or carcinoma$ or metastas$)).tw.
7. or/4-6
8. 3 and 7
9. randomized controlled trial.pt.
10. controlled clinical trial.pt.
11. randomized controlled trials/
12. random allocation/
13. double blind method/
14. single blind method/
15. or/9-14
16. clinical trial.pt.
17. exp clinical trials/
18. (clin$ adj25 trial$).ti,ab.
19. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
20. placebos/
21. placebos.ti,ab.
22. random.ti,ab
23. research design/
24. or/16-23
25. comparative study/
26. exp evaluation studies/
27. follow up studies/
28. (control$ or prospectiv$ or volunteer$).ti,ab.
29. prospective studies/
30. or/25-29
31. 15 or 24 or 30
32. 8 and 31
33. from 32 keep 1-81

Appendix 2. Additional search strategies

Database searched	Search strategy
The Cochrane Database of Systematic Reviews	#1 ((best in All Text near/3 support* in All Text) or (optim* in All Text near/3 support* in All Text) or (support* in All Text near/3 care* in All Text) or (support* in All Text near/3 caring in All Text)) #2 MeSH descriptor GASTROINTESTINAL NEOPLASMS explode all trees #3 ((gastrointestinal in All Text or gastro-intestinal in All Text or (esophageal in All Text and oesophageal in All Text) or pancrea* in All Text or gastric in All text or stomach in All Text or intestin* in All Text or cecal in All Text or appendiceal in All Text or colorectal in All Text or colonic in All Text or sigmoid in All Text or rectal in All Text or anus in All Text or "anal gland" in All Text) and (neoplasm* in All Text or cancer* in All Text or tumor* in All Text or tumour* in All Text or carcinoma* in All Text or malignan* in All Text or metastas* in All Text)) #4 MeSH descriptor PANCREATIC NEOPLASMS explode all trees #5 (#2 or #3 or #4) #6 (#1 and #5)
Cochrane Sensitive Search strategy for RCTs	1. randomized controlled trial.pt. 2. controlled clinical trial.pt. 3. randomized controlled trials.sh. 4. random allocation.sh. 5. double blind method.sh. 6. single blind method.sh. 7. or/1-6 8. (ANIMALS not HUMAN).sh. 9. 7 not 8 10. clinical trial.pt. 11. exp clinical trials/ 12. (clin$ adj25 trial$).ti,ab. 13. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 14. placebos.sh. 15. placebo$.ti,ab. 16. random$.ti,ab. 17. research design.sh. 18. or/10-17 19. 18 not 8 20. 19 not 9 21. 9 or 19
EMBASE via Ovid	1. ((best adj3 support$) or (optim$ adj3 support$) or (support$ adj3 care$) or (support$ adj3 caring) or (supportive adj3 treatment$)).mp. [mp=title, subject heading word, abstract, instrumentation] 2. Gastrointestinal Tumor/ or Gastrointestinal Stromal Tumor/ 3. exp Pancreas Tumor/ 4. ((gastrointestinal or gastro-intestinal or esophageal or oesophageal or pancrea$ or gastric or stomach or intestin$ or cecal or appendiceal or colorectal or colonic or sigmoid or rectal or anus or "anal gland") and (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or malignan$ or metastas$)).mp. [mp=title, subject heading word, abstract, instrumentation] 5. or/2-4 6. 1 and 5
The above subject search was linked to the following Filter for EMBASE via OVID	1. random$.ti,ab. 2. factorial$.ti,ab. 3. (crossover$ or cross over$ or cross-over$).ti,ab. 4. placebo$.ti,ab. 5. (doubl$ adj blind$).ti,ab. 6. (singl$ adj blind$).ti,ab. 7. assign$.ti,ab. 8. allocat$.ti,ab. 9. volunteer$.ti,ab. 10. CROSSOVER PROCEDURE.sh. 11. DOUBLE-BLIND PROCEDURE.sh.

(Continued)

	12. RANDOMIZED CONTROLLED TRIAL.sh. 13. SINGLE BLIND PROCEDURE.sh. 14. or/1-13 15. ANIMAL/ or NONHUMAN/ or ANIMAL EXPERIMENT/ 16. HUMAN/ 17. 16 and 15 18. 15 not 17 19. 14 not 18
CINAHL Search Strategy (As MEDLINE)	1. Random Assignment/ 2. single-blind studies/ 3. Double-Blind Studies/ 4. Triple-Blind Studies/ 5. Crossover Design/ 6. Factorial Design/ 7. (multicentre study or multicenter study or multi-centre study or multi-center study).mp. [mp=title, cinahl subject headings, abstract, instrumentation] 8. random$.ti,ab. 9. latin square.ti,ab. 10. cross-over.mp. or crossover.ti,ab. [mp=title, cinahl subject headings, abstract, instrumentation] 11. Placebos/ 12. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 13. placebo$.mp. [mp=title, cinahl subject headings, abstract, instrumentation] 14. Clinical Trials/ 15. (clin$ adj25 trial$).mp. [mp=title, cinahl subject headings, abstract, instrumentation] 16. or/1-15
PsycINFO Search Strategy	1. ((best adj3 support$) or (optim$ adj3 support$) or (support$ adj3 care$) or (support$ adj3 caring) or (supportive adj3 treatment$)).mp. [mp=title, abstract, heading word, table of contents, key concepts] 2. ((gastrointestinal or gastro-intestinal or esophageal or oesophageal or pancrea$ or stomach or intestin$ or cecal or appendiceal or colorectal or colonic or sigmoid or rectal or anus or "anal gland") and (neoplasm$ or cancer$ or tumor$ or tumour$ or carcinoma$ or malignan$ or metastas$)).mp. [mp=title, abstract, heading word, table of contents, key concepts] 3. 1 and 2

WHAT'S NEW

Date	Event	Description
7 October 2009	New search has been performed	This is an update. The search was re-run in July 2009 and no further studies were added to the most recent publication of this review, therefore the conclusions remain the same.
7 October 2009	Review declared as stable	This review no longer requires an update as evidence is unlikely to become available. In the event that new evidence does become available the review will be updated again.

HISTORY

Protocol first published: Issue 1, 2002
Review first published: Issue 3, 2004

Date	Event	Description
29 July 2008	Amended	Converted to new review format.
1 July 2006	New search has been performed	This is an update of the original review published in 2004. No new studies were included or excluded for this version updated for Issue 4, 2006 and the conclusions remain the same.

CONTRIBUTIONS OF AUTHORS

Tasks and responsibilities were shared amongst the systematic review team for the first version of the review. For both of the updates Nisar Ahmed checked for any new studies, none of which were identified.

DECLARATIONS OF INTEREST

None known. The involvement of the Advisory Group should serve to limit any potential conflict of interest during the review process.

SOURCES OF SUPPORT

Internal sources

- The University of Sheffield, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

*Palliative Care; Gastrointestinal Neoplasms [drug therapy] [*therapy]; Quality of Life; Randomized Controlled Trials as Topic

MeSH check words

Humans