FINAL REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Systematic review to examine the clinical effectiveness and tolerability of chemotherapy treatment for older people with colorectal cancer

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Title: Systematic review to examine the clinical effectiveness and tolerability of chemotherapy treatment for older people with colorectal cancer

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Abbreviations:

AC	Doxorubicin plus cyclophosphamide
aCRC	Advanced colorectal cancer
ADL	Activities of Daily Living
AE	Adverse event
CALGB	Cancer and Leukemia Group B
CAPIRI/XELIRI	Capecitabine plus irinotecan
CAPOX/XELOX	Capecitabine plus oxaliplatin
CCI	Charlson Comorbidity Index
CGA	Comprehensive geriatric assessment
CI	Confidence interval
CRC	Colorectal cancer
CIRS-G	Cumulative Illness Rating Scale for Geriatrics
CTP-11	Irinotecan
DDC	Duration of disease control
DFS	Disease-free survival
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EORTC-QLQ-C30	EORTC Quality of Life Cancer Questionnaire
FA	Folinic acid (leucovorin)
FAP	Familial adenomatous polyposis
FOLFIRI	5-fluorouracil plus leucovorin and irinotecan
FOLFOX/FUFOX	5-fluorouracil plus oxaliplatin and leucovorin
FUOX	5-fluorouracil plus oxaliplatin
GDS	Geriatric Depression Scale
HNPCC	Hereditary non polyposis colorectal cancer
HR	Hazard ratio
IADL	Instrumental Activities of Daily Living
IFL	Irinotecan plus leucovorin and fluorouracil
IPD	Individual patient data
ITT	Intention to treat
KPS	Karnofsky performance status
LV	Leucovorin
Mcrc	Metastatic colorectal cancer
MGA	Multidimensional Geriatric Assessment
MMS	Mini-Mental Status
MMSE	Min-Mental State Examination
MST	Mean survival time
NCEI	The National Cancer Equity Initiative
NR	Not reported
ORR	Objective response rate
OS	Overall survival
PFS	Progression–free survival
POI	Pharmaceutical Oncology Initiative
PS	Performance status
QoL	Quality of life
RCT	Randomised controlled trial

RDI	Relative dose intensity
RFS	Relapse–free survival
SD	Standard deviation
TNM	Tumour, Node, Metastases
TTF	Time to treatment failure
TTP	Time to disease progression
WHO	World Health Organisation
XELIRI/CAPIRI	Capecitabine plus irinotecan
XELOX/CAPOX	Capecitabine plus oxaliplatin
5-FU	5-fluorouracil

Definition of terms:

Biological therapy	Treatments that use natural substances from the body, or drugs made from these substances, to fight cancer or to lessen the side-effects that may be caused by some cancer treatments
Chemotherapy	The treatment of cancer with cytotoxic anti-cancer drugs
Heterogeneity	In statistics this means that there is between-study variation. If heterogeneity exists the pooled effect size in a meta-analysis has no meaning, as the presence of heterogeneity indicates that there is more than one true effect size in the studies being combined

Please note that the abbreviations and drug combinations shown above and in the tables throughout the report have been described as reported by the study authors rather than being standardised across this review.

1 EXECUTIVE SUMMARY

1.1 Background

Older people with cancer are less likely to receive radical treatment for their disease, due to comorbidities and/or frailty associated with old age, and uncertainty over the tolerability of chemotherapy treatment in older patients. The National Cancer Equity Initiative (NCEI) is focussed on reducing cancer inequalities, which includes improving outcomes for older patients with cancer. In collaboration with the Pharmaceutical Oncology Initiative (POI), the NCEI is seeking to deepen the understanding of current practice in relation to cancer treatment for older people, with the aim of enabling a more personalised treatment protocol, which takes into account fitness, choice and benefit to the individual.

1.2 Aims and objectives

The aim of this review is to systematically consider the evidence for the clinical effectiveness and tolerability of chemotherapy regimens used to treat colorectal cancer in older people.

1.3 Methods

Search strategy

Four electronic databases (MEDLINE, EMBASE, The Cochrane Library and Web Of Knowledge) were searched from January 2000 to May 2013.

Study selection

The references identified were assessed for inclusion through two stages. In stage 1, two reviewers independently screened all relevant titles and abstracts identified via electronic searching and selected potentially relevant studies for inclusion in the review. In stage 2, full-text copies of the potentially relevant studies were obtained and assessed independently by two reviewers. Any disagreements between reviewers were resolved by discussion with a third reviewer at each stage. Studies that did not meet the inclusion criteria at stage 2 were excluded.

Data extraction and quality assessment strategy

Data extraction forms were developed and piloted in an Excel spreadsheet using a sample of included studies, and adapted to reflect the nature of both randomised controlled trials (RCTs) and non-randomised studies. Data were extracted on study design, population characteristics and outcomes by one reviewer and independently checked for accuracy by a second reviewer, with disagreements resolved through discussion with a third reviewer where necessary.

Evidence synthesis

Due to the heterogeneity of the included studies and limited data, it was not possible or appropriate to perform any statistical analyses. The results of the data extraction and quality assessment exercises for each study are presented in structured tables and as a narrative summary.

1.4 Results

Electronic searching of databases resulted in 352 references. Manual de-duplication of references resulted in 346 unique references for screening at stage 1.

Initial screening of titles and abstracts identified 191 references, which were obtained as full-text papers. A total of 111 references (85 studies) met the inclusion criteria at stage 2 and were included in the review.

The review included data from two RCTs, 10 subgroups of RCTs, seven pooled analyses, 49 single cohort studies and 17 retrospective studies.

1.5 Conclusions

There is a distinct lack of good-quality research into the treatment of older patients with colorectal cancer. Chemotherapy may be effective in treating older patients with colorectal cancer, and although older patients are at risk of higher adverse events, treatment with chemotherapy appears to be tolerable. Treatment should not routinely be withheld from older patients, and older patients should be given the opportunity to discuss treatment options with healthcare professionals, taking into account factors including fitness, comorbidities and personal choice.

2 BACKGROUND

Older people with cancer are less likely to receive radical treatment. There are a number of reasons for this, including comorbidities and/or frailty associated with older age, and a complex mix of factors affecting patient or clinician choice. There is also uncertainty about the tolerability of chemotherapy treatment in older patients. However, not all older people are frail; many have good life expectancy and are in good health overall. There is evidence to suggest that characteristics other than age are not fully assessed when treating older people with cancer, some of whom may be able to tolerate effective treatment.

The National Cancer Equity Initiative (NCEI) is focussed on reducing cancer inequalities, which includes improving outcomes for older patients with cancer. In collaboration with the Pharmaceutical Oncology Initiative (POI), the NCEI is seeking to deepen the understanding of current practice in relation to cancer treatment for older people, with the aim of enabling a more personalised treatment protocol, which takes into account fitness, choice and benefit to the individual.

Older patients are underrepresented in clinical trials, and those who are included do not generally have the same characteristics as older people treated in routine clinical practice. This is due to the enrolment of fitter and healthier patients in trials. As a result, there are limited data on the efficacy and tolerability of chemotherapy for this patient population seen in the UK National Health Service (NHS).

2.1 Description of health problem

Colorectal cancer (CRC), which is also known as bowel, colon or rectal cancer, refers to cancer that forms in the large intestine or rectum. Approximately two-thirds of all bowel cancers are cancers of the colon.[1] Colorectal cancer is the fourth most common cancer in the UK[2], with 41,581 new diagnoses in the UK in 2011.[1] The majority of diagnoses are in older people: 95% are in people aged over 50, and 43% in those aged over 75 years.[1] Colorectal cancer is the second most common cause of cancer deaths in the UK, and 57% of deaths caused by CRC in the UK are in patients aged over 75 years.[3]

There are four main types of CRC: 95% of CRCs diagnosed are adenocarcinomas (the cancer starts in the gland cells in the bowel wall), squamous cell cancers (squamous cells are skin-like cells in the bowel lining), carcinoid tumours (cancer cells that grow in hormone-producing tissues in the digestive system), and sarcomas (cancers that begin in smooth muscle).[4]

2.1.1 Aetiology

The risk of CRC increases with age; however, there are other factors that increase a person's risk of developing CRC, such as a family history of the disease, the inherited conditions of familial

adenomatous polyposis (FAP) and hereditary non-polyposis CRC (HNPCC), the presence of benign polyps in the bowel that may develop into cancer, and ulcerative colitis and Crohn's disease.[2] In the UK in 2011, 56% of CRC cases were in men and 44% were in women.

2.1.2 Pathology and prognosis

There are two staging systems used when diagnosing CRC in the UK: Dukes' staging and the TNM (Tumour, Node, Metastases) system. Dukes' A indicates that the cancer is in the innermost lining of the colon/rectum, B indicates cancer in the muscle of the colon/rectum, C indicates that the cancer has spread to nearby lymph nodes and D indicates metastatic disease that has spread to other parts of the body.[5] The TNM system is a numbered staging system: stage 0 (cancer in situ) refers to cancer cells that are found in the inner bowel lining, stage 1 refers to cancer that has spread to the muscle of the colon/rectum, stage 2 refers to cancer that has spread to the bowel wall or tissue next to the bowel, stage 3 indicates a spread of cancer cells to lymph nodes or surrounding tissue/organs, and stage 4 indicates cancer that has spread to other parts of the body.[5]

Table 1 Disease staging

Dukes'	TNM
A – the cancer is in the innermost lining of the colon/rectum	Stage 0 (cancer in situ) – the cancer cells are found in the inner bowel lining
B – the cancer is in the muscle of the colon/rectum	Stage 1 – the cancer has spread to the muscle of the colon/rectum
C – the cancer has spread to nearby lymph nodes	Stage 2 – the cancer has spread to the bowel wall or tissue next to the bowel
D – metastatic disease – the cancer has spread to other parts of the body	Stage 3 – the cancer has spread to lymph nodes or surrounding tissue/organs
	Stage 4 – metastatic disease – the cancer has spread to other parts of the body

The outlook for those diagnosed with early-stage cancer who can be treated with surgery is good, with approximately 93% of patients surviving for 5 years.[6] This figure reduces for patients diagnosed with stage 2 and 3 disease, which account for 47% of diagnoses, with 5-year survival rates of 77% and 48%, respectively. For patients diagnosed with stage 4 disease, only 6% will live for 5 years.[6]

2.1.3 Current treatment options

Treatment for CRC depends on the type and stage of the disease together with a patient's general health. Surgery is the mainstay of treatment for early-stage cancer, and chemotherapy and/or radiotherapy (rectal cancer) can be used as an adjuvant therapy. For advanced disease, treatment is less likely to be curative. Treatment is usually palliative and could include chemotherapy, biological therapy and radiotherapy.[7] Supportive care is also an essential component of a patient's treatment throughout their treatment pathway.

3 AIMS AND OBJECTIVES

3.1 Objectives

The aim of this review is to systematically consider the evidence for the clinical effectiveness and tolerability of chemotherapy regimens used to treat CRC in older people. The review forms part of a larger project, which focusses on six types of cancer in older populations: breast, colorectal, lung, renal cell, chronic myeloid leukaemia and non-Hodgkin's lymphoma. The final report will consist of the results of a systematic review of the literature in each of these six clinical areas.

The objectives of this review are to:

- systematically review and summarise the relevant evidence related to clinical effectiveness and tolerability of treatment
- explore the implications of these findings for practice and service provision in order to disseminate accessible information to clinicians
- inform future decisions on research priorities through the identification of gaps and weaknesses in the available evidence.

3.2 Inclusion considerations

The population of interest is older people with CRC. There is no agreed definition of 'older': The World Health Organisation[8] states that most countries of the developed world have accepted the chronological age of 65 years as a definition of 'elderly' or 'older', whereas the British Geriatrics Society[9] describes geriatric medicine as being mainly concerned with people aged over 75. We have therefore focussed on published studies that specifically describe their patients or subgroups of patients, as 'older' or 'elderly'. In order to obtain a comprehensive dataset, no restrictions have been made with regard to the stage of disease, tumour histology or the line of treatment.

All forms of chemotherapy (defined as a systemic anti-cancer therapy) have been considered. To ensure that the most recent treatments are included it was decided, in consultation with clinical experts, to also consider targeted biological therapies, based on the premise that the two treatment types tend to be considered equally effective in clinical practice.

4 METHODS

4.1 Search strategy

Four electronic databases (MEDLINE, EMBASE, The Cochrane Library and Web Of Knowledge) were searched from January 2000 to May 2013, and all references were exported to EndNote® version X4. A comprehensive search strategy was employed and is included in Appendix 1.

4.2 Study selection

The references identified were assessed for inclusion through two stages. In stage 1, two reviewers independently screened all relevant titles and abstracts identified via electronic searching and selected potentially relevant studies for inclusion in the review. In stage 2, full-text copies of the potentially relevant studies were obtained and assessed independently by two reviewers using the inclusion criteria outlined in Table 2. Any disagreements between reviewers were resolved by discussion with a third reviewer at each stage. Studies that did not meet the inclusion criteria at stage 2 were excluded.

Table 2 Inclusion criteria

Study design	Randomised controlled trials; systematic reviews; cohort studies, including retrospective studies of databases and registries
Patient population	Older people (older as defined by study authors) treated for CRC
Interventions	Any chemotherapy (all lines of treatment)
Comparators	• an alternative chemotherapy or • best supportive care
Outcomes	Efficacy outcomes: • overall survival • progression-free survival • response rates Tolerability outcomes: • adverse events • tolerability Other outcomes: • quality of life • comprehensive geriatric assessment
Other considerations	Papers that reported subgroup analyses for older people in their abstract were included Only studies published since 2000 in full or with an English language abstract were included

4.2.1 Outcomes

The majority of outcomes presented in this review are commonly used measures of survival or response to treatment; however, 'tolerability' and 'comprehensive geriatric assessment' (CGA) may require further explanation.

Tolerability

In order to determine whether or not older patients can tolerate chemotherapy treatment, it was necessary to gather evidence from a range of outcomes. One measure of tolerability is a patient's adherence to the treatment regimen and/or how much of the treatment was received. Common

measures reported in studies are the mean or median number of cycles delivered per patient, how many people completed the treatment and the relative dose intensity (RDI) of treatment. Therefore, data were extracted from any measure that could be used to determine how much treatment a patient received.

Treatment discontinuations and withdrawals are other measures of how well a patient has tolerated chemotherapy. Therefore, any data relating to discontinuation due to toxicity, withdrawal of consent, disease progression or death were extracted.

Many studies report the number of patients whose dose of treatment was modified or interrupted due to adverse events (AEs), which again is a good measure of how well a treatment is tolerated. Any data that encompassed modifications or interruptions in treatment were extracted.

Randomised controlled trials (RCTs) commonly report AEs, and therefore all reported AEs of grade 3 or higher that occurred in more than 10% of patients in each arm were included in data extraction, together with any information on toxic deaths.

Comprehensive geriatric assessment

Comprehensive geriatric assessment is often carried out to determine an older person's health, both physical and mental, in order to decide on the appropriate treatment pathway for the individual. There are numerous tools used by clinicians, and studies often use CGA to determine eligibility for trials or as an outcome measure to establish how well the patient has responded to treatment in terms of how fit and well they are. Where available, CGA-related data were extracted.

4.3 Data extraction and quality assessment strategy

Data extraction forms were developed and piloted in an Excel spreadsheet using a sample of included studies, and then adapted to reflect the nature of both RCTs and non-randomised studies. Data were extracted on study design, population characteristics and outcomes by one reviewer and independently checked for accuracy by a second reviewer, with disagreements resolved through discussion with a third reviewer where necessary.

Included RCTs were assessed for methodological quality using criteria based on the Centre for Reviews and Dissemination guidance.[10] Data relating to quality assessment were extracted by one reviewer and independently checked for accuracy by a second reviewer. Where necessary, disagreements between reviewers were discussed in consultation with a third reviewer to achieve consensus. Full details of the quality assessment criteria used are provided in Appendix 2.

No universally accepted standardised quality assessment tool exists for use in non-randomised studies. There are a multitude of study designs and so, even where tools exist, applying them is problematic

and of limited value. Due to the nature of the study designs of the included non-randomised studies, it was difficult to extract or compare information in a meaningful and relevant manner. Therefore, we made the pragmatic decision not to quality assess the non-randomised studies.

4.4 Evidence synthesis

Due to the heterogeneity of the included studies and insufficient data, it was not possible or appropriate to perform any statistical analyses. The results of the data extraction and quality assessment for each study are presented in structured tables and as a narrative summary.

5 QUANTITY AND QUALITY OF RESEARCH AVAILABLE

5.1 Number of studies identified

Electronic searching of databases resulted in 352 references. Manual de-duplication of references resulted in 346 unique references for screening at stage 1. See Figure 1 for details.

Initial screening of 346 titles and abstracts identified 191 references, which were obtained as full-text papers (stage 1). A total of 111 references (85 studies) met the inclusion criteria at stage 2 and were included in the review. A list of references that were excluded at stage 2 is presented in Appendix 3. The 85 studies included in the review were divided into six categories, based on study design. Table 3 presents the number of studies in each category and a brief description of the study type.

Table 3 Categorisation of included studies

Study type	Definition	Number of studies
RCT	RCTs recruiting only patients defined as elderly/older	2
Subgroup analyses of RCTs	Analyses of RCTs from the general population with elderly/older subgroups reported separately	10
Pooled analyses	Published studies that use aggregated subgroup data on elderly/older patients from RCTs or cohort studies	7
Single cohorts	Studies that report single cohorts of elderly/older patients	49
Retrospective data	Any reports of chemotherapy treatment for elderly/older patients in a defined cohort of patients or as report from registries of patient outcomes	17
Total		**85**

RCT=randomised controlled trial

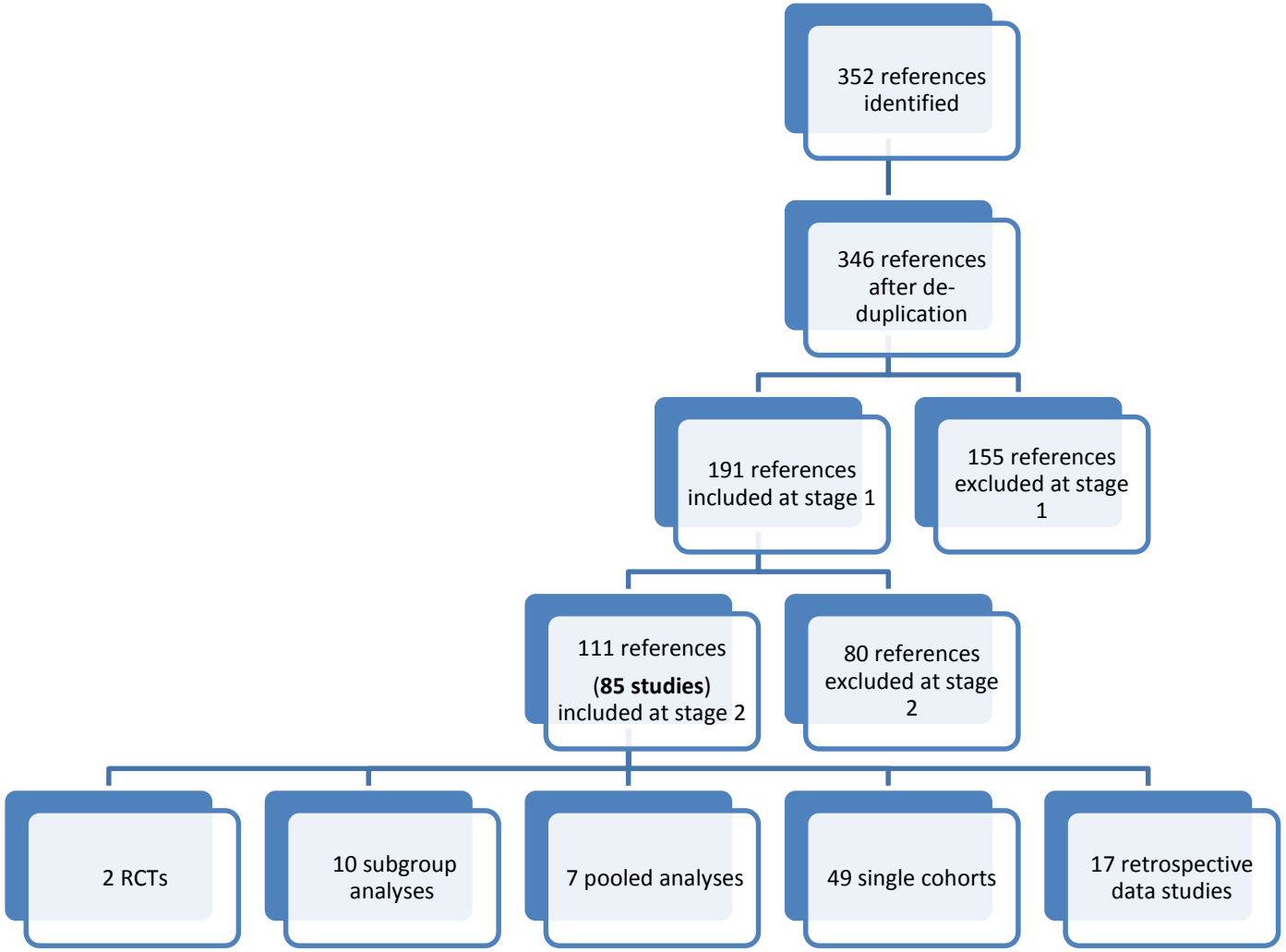

Figure 1 Flow diagram of included studies

6 RANDOMISED CONTROLLED TRIALS

Two RCTs[11,12] that enrolled only older patients met the inclusion criteria and were included in the review. Results for the quality assessment exercise are presented in Table 4, and study characteristics are presented in Table 5. The publication by Aparicio et al[11] was available in abstract form only.

6.1 Quality assessment

Of the two included RCTs[11,12] only one[12] was published in full and presented sufficient information for assessment of methodological quality.

The trial[12] was assessed as being truly random, but there was insufficient information to determine whether there was adequate concealment of allocation or whether patients and assessors were blinded or not. Baseline data were presented, and trials arms were comparable. The trial utilised an intention-to-treat (ITT) analysis, with more than 80% of patients included in the final analysis. The trial also included information regarding the statistical powering of the analyses conducted.

Table 4 Quality assessment, randomised controlled trials

Study	Randomisation			Baseline comparability		Eligibility criteria specified	Co-interventions identified	Blinding				Withdrawals		Other measures	ITT	Powering
	Truly random	Allocation concealment	Number stated	Baseline presented	Baseline achieved			Assessors	Administrators	Participants	Procedure assessed	>80% in final analysis	Reasons stated			
Rosati 2010[12]	✓	?	✓	✓	✓	✓	?	?	?	?	?	✓	✓	✕	✓	✓

Items are graded in terms of ✓ yes (item properly addressed), ✕ no (item not properly addressed), or **?** unclear/not enough information
ITT=intention to treat

6.2 Study characteristics

Both of the included RCTs[11,12] were multicentre studies; Rosati et al[12] was a phase II trial conducted in Italy, and Aparicio et al[11] was a phase III trial, although study location was not reported. The trials[12,13] were conducted between 2003 and 2010. The largest trial was Aparicio et al,[11] which randomised 123 patients; Rosati et al[12] randomised 94 patients.

Both trials[11,12] focussed on the first-line treatment of patients with metastatic CRC (mCRC). The cut-off age for trial entry was ≥75 years[11] and >70 years,[12] with Aparicio et al[11] reporting the highest median age (80 years). Aparicio et al[11] investigated the use of fluorouracil (5-FU)-based chemotherapy, with or without the addition of irinotecan, and Rosati et al[12] investigated capecitabine plus oxaliplatin (CAPOX) versus capecitabine plus irinotecan (CAPIRI).

The proportion of males in each study was similar; Aparicio et al[11] reported an overall figure of 54% and Rosati et al[12] reported 53% for each arm. Performance status (PS) was reported for both trials;[11,12] the proportion of fitter patients in Aparicio et al[11] (Karnofsky performance status [KPS] 90-100) was lower than the proportion of fitter patients (WHO 0) in Rosati et al.[12]

Table 5 Study characteristics, randomised controlled trials

Study	Details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
Aparicio 2011[11] (abstract only)	Phase III Multicentre 2003-2010	mCRC First-line Aged ≥75 years (n=123)	5-FU-based chemotherapy plus irinotecan (50.4%)	Median age: 80 years (75-91) Males: 54% KPS: 60-70=32%, 80-90=32%, 100=36%	Toxicity and dose intensity	For the first time in a randomised prospective phase III study in mCRC, geriatric factors (MMSE and IADL) are predictive of severe toxicities or dose-intensity reduction. These results suggest that cognitive function and autonomy impairment should be considered
			5-FU-based chemotherapy (49.6%)			
Rosati 2010[12]	Phase II Multicentre Italy Median follow-up 18 months 2005-2008	Metastatic or locally advanced CRC First-line Aged >70 years (n=94)	CAPOX (n=47)	Median age: 75 years (70-85) Males: 53% WHO PS: 0=51%, 1=45%, 2=4% Tumour site: colon=64%, rectum=17%	Primary outcome: activity Secondary: safety, TTP, OS, QoL	CAPOX and CAPIRI had similar efficacy in elderly patients, although CAPOX seemed to be better tolerated
			CAPIRI (n=47)	Median age: 74 years (70-90) Males: 53% WHO PS: 0=60%, 1=38%, 2=2% Tumour site: colon=57%, rectum=20%		

PS=performance status; KPS=Karnofsky Performance Status; WHO=World Health Organisation; mCRC=metastatic colorectal cancer, MMSE=Mini-Mental State Examination; IADL=Independent Activities of Daily Living; 5-FU=5-fluorouracil; CAPOX=Capecitabine plus oxaliplatin; CAPIRI=capecitabine plus irinotecan TTP=time to progression, OS=overall survival; QoL=quality of life

6.3 Efficacy evidence

Only one trial[12] reported efficacy outcomes of interest. Details are presented in Table 6.

Rosati et al[12] reported data for progression-free survival (PFS), median survival time (MST) and objective response rate (ORR); however, none of the results were statistically significant. The CAPOX regimen achieved a slightly longer PFS than the CAPIRI regimen (median 8 months [95% confidence interval (CI) 3 to 13] vs 7 months [95% CI 6 to 8]). The CAPOX regimen also achieved longer MST (19.3 months [95% CI 10.8 to 27.7] vs 14 months [95% CI 9.5 to 18.4]). The ORR was similar in each arm, with CAPOX achieving a slightly higher rate (38%) compared with CAPIRI (36%).

Table 6 Efficacy evidence, randomised controlled trials

Study	Intervention	Median PFS (95% CI) Months	Hazard ratio (95% CI) p value	MST (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
Rosati 2010[12]	CAPOX	8 (3 to 13)	p=0.195	MST 19.3 (10.8 to 27.7)	p=0.165	38 (24 to 53)	p=0.831
	CAPIRI	7 (6 to 8)		MST 14.0 (9.5 to 18.4)		36 (22 to 50)	

CAPOX=capecitabine plus oxaliplatin; CAPIRI=capecitabine plus irinotecan; MST=median survival time; ORR=objective response rate; PFS=progression-free survival; CI=confidence interval

6.4 Tolerability evidence

Both RCTs[11,12] reported at least one outcome of interest for tolerability outcomes. Details are presented in Table 7.

Rosati et al[12] reported a median of 6 (1 to 12) cycles per patients in the CAPOX arm, compared with 5 (1 to 14) in the CAPIRI arm. More patients in the CAPIRI arm discontinued treatment due to toxicity (23% vs 9%).[12] Both trials[11,12] reported dose reductions. Aparicio et al[11] reported dose reductions of 66% for 5-FU with/without irinotecan (33% during the first 4 months), and Rosati et al[12] reported 13% and 11% reductions for CAPOX and CAPIRI, respectively.

Adverse events were reported for both trials. Aparicio et al[11] reported an overall figure of 58% for any grade 3-4 AE. Rosati et al[12] reported rates of grade 3-4 diarrhoea (CAPIRI, 32%; CAPOX, 15%), which were not significantly different (p=0.052), but rates of grade 3-4 neutropenia (CAPIRI, 23%; CAPOX 6%) were significantly different (p=0.021).

Table 7 Tolerability evidence, randomised controlled trials

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Aparicio 2011[11] (abstract only)	NR	NR	5-FU with/without irinotecan: Dose reduction=66% Dose reduction during first 4 months=33%	Any grade 3-4=58%
Rosati 2010[12]	CAPOX: Median cycles per patient=6 (range 1-12)	Discontinued due to toxicity=9%	Interruption after cycle 1=2% (due to AEs and no clinical benefit) Oxaliplatin dose reduction=26%: 80% dose=24%, 60% dose=2% Oxaliplatin and capecitabine dose reduction=13%	Diarrhoea=15% Neutropenia=6% Neurosensory=15% 1 death due to myocardial infarction during cycle 2
	CAPIRI: Median cycles per patient=5 (range 1-14)	Discontinued due to toxicity=23%	Interruption after cycle 1=6% (due to AEs and no clinical benefit) Irinotecan dose reduction=38%: 80% dose=30%, 60% dose=8% Irinotecan and capecitabine dose reduction=11%	Diarrhoea=32% (CAPOX vs CAPIRI; p=0.052) Neutropenia=23% (CAPOX vs CAPIRI; p=0.021) 1 death due to sepsis/febrile neutropenia during cycle 1

CAPOX=capecitabine plus oxaliplatin; CAPIRI=capecitabine plus irinotecan; 5-FU=5-fluorouracil ;AE=adverse event; NR=not reported

6.5 Comprehensive geriatric assessment and quality of life

Summary details of outcomes relating to CGA and quality of life (QoL) are presented in Table 8.

6.5.1 Comprehensive geriatric assessment

Aparicio et al[11] used four CGA tools to determine how many patients fulfilled the geriatric score at baseline, and as a variable to predict toxicity. The tools used were: Charlson Comorbidity Index (CCI), Mini-Mental State Examination (MMSE), Instrumental Activities of Daily Living (IADL), and the Geriatric Depression Scale (GDS).

6.5.2 Quality of life

Rosati et al[12] utilised the European Organisation for Research and Treatment of Cancer Questionnaire (EORTC QLQ-C30) to measure QoL, and found that response to treatment and AEs did not substantially influence changes in QoL.

Table 8 Comprehensive geriatric assessment and quality of life, randomised controlled trials

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Author conclusions**
Aparicio 2011[11] (abstract only)	CCI MMSE IADL GDS	CGA was used to determine how many patients fulfilled the geriatric score at baseline, and as a variable to predict toxicity	NR	NR
Rosati 2010[12]	NR	NR	EORTC QLQ-C30	Neither response to treatment nor occurrence of side-effects substantially influenced changes in patients quality of life

CCI=Charlson Comorbidity Index; MMSE=Mini–Mental State Examination; IADL=Instrumental Activities of Daily Living; GDS=Geriatric Depression Scale; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; CGA=comprehensive geriatric assessment; NR=not reported

6.6 Summary and discussion

Two RCTs[11,12] met the inclusion criteria and were included in the review. One RCT[11] was published in abstract form only and was therefore not assessed for methodological quality. The trial that was published in full[12] was assessed as being of reasonable methodological quality.

One trial[11] investigated the use of first-line 5-FU-based chemotherapy, with or without the addition of irinotecan, and the other trial[12] investigated first-line CAPOX versus CAPIRI. Both trials[11,12] were relatively small, with 94[12] and 123[11] patients randomised. Both trials focussed on treating patients with mCRC.

One trial[12] reported efficacy outcomes, and found that CAPOX performed slightly better than CAPIRI; however, none of the results were statistically significant. Both trials[11,12] reported outcomes relating to tolerability. Rosati et al[12] reported higher rates of AEs in the CAPIRI arm, with a statistically significant result for neutropenia (p=0.021).

One trial[11] reported the use of a CGA tool, which measured the proportion of patients meeting the geriatric score at baseline. The other trial[12] reported outcomes for the use of a QoL measure.

7 SUBGROUP ANALYSES OF RANDOMISED CONTROLLED TRIALS

Ten studies (reported in 13 publications[13-25]) that reported subgroup analyses of older patients from RCTs were included in the review. Study characteristics are presented in Table 9.

7.1 Study characteristics

Seven studies[13,17-23] reported data derived from phase III RCTs, one study[14-16] reported data derived from a phase II/III RCT, one study[25] reported data derived from a phase I RCT, and the phase was not reported in one study.[24] Seven studies[13-18,20,21,23,24] were multicentre, and four studies[13,17,18,23,24] were international.

Four of the included studies[14-18,21,22] were funded by pharmaceutical companies, and six studies[13,19,20,23-25] did not report funding information. Two studies[21,24] reported that patients were stratified by age at randomisation, three studies[22,23,25] reported that patients were not stratified by age, and five studies[13-20] did not report information regarding the stratification of patients.

Six studies[13-16,21,23-25] enrolled patients with mCRC, two studies[19,22] enrolled patients with advanced CRC (aCRC) and two studies[17,18,20] enrolled patients with stage II/III disease. Five studies[17,18,21-24] focussed on first-line treatment, two studies[13,19] were second-line and four studies[14-16,20,23,25] did not report the line of treatment. The proportion of older patients included in the studies ranged from 6%[24] to 44%.[13,25] Where available, the median age of older patients ranged from 73 years[22] to 80.2 years.[14-16] The characteristics of older and younger patient subgroups were not always fully reported.

The conclusions of the study authors suggest that chemotherapy regimens are effective and tolerable for older patients with CRC, and that outcomes are comparable with those seen in younger patients.

Table 9 Study characteristics, subgroups of randomised controlled trials

Study	Details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
Bouche 2012[13] (abstract only)	Phase III Multicentre Austria, Belgium, Czech Republic, Denmark, Estonia, Finland, France, Germany, The Netherlands, Norway, Portugal, Saudi Arabia, Spain, Sweden, and Switzerland Bevacizumab follow-up 11.1 months CT[a] follow-up 9.6 months 2006-2010	mCRC Second-line ≥65=44%	Fluoropyrimidine-based chemotherapy plus bevacizumab n=409	Median age: 63 years (27-84) ECOG PS: 0=44%, 1=51%, 2=5%	Efficacy, safety	This subgroup analysis of ML18147 suggests that the addition of bevacizumab to chemotherapy after disease progression improves PFS and OS in patients <65 years and ≥65 years of age. The incidence of grade 3-5 AEs was similar within age groups
			Fluoropyrimidine-based chemotherapy n=411	Median age: 63 years (21-84) ECOG PS: 0=43%, 1=52%, 2=5%		
Price 2012[14-16]	Phase II/III Multicentre Australia Funded by Roche Australia	mCRC ≥75=21% (n=471)	Capecitabine (n=37)	Median age: 78.7 years (75.2-86) Male: 70% ECOG PS: 0-1=92%	Tolerability, dose intensity	Addition of bevacizumab to capecitabine significantly improved PFS in this geriatric population, with similar benefits to those aged <75 years. Treatment was well tolerated with no signal of increased toxicity (including thromboembolism) when compared with those aged <75 years
			Capecitabine plus bevacizumab (n=32)	Median age: 78.7 years (75-84.9) Male: 75% ECOG PS: 0-1=88%		
			Capecitabine plus bevacizumab and mitomycin C (n=30)	Median age: 80.2 years (75.2-83.8) Male: 53% ECOG PS: 0-1=83%		
Twelves 2012[17,18]	Phase III Multicentre UK, Austria, Australia,	Stage III CRC First-line	Capecitabine (52.5%)	Median age: 62 years (25-80)	DFS, OS, RFS	Oral capecitabine is an effective alternative to bolus 5-FU plus FA as

Study	Details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
	France, Canada, Spain, Switzerland Median follow-up 6.9 years 1998-2001 Funded by Roche	≥70=19.9% (n=1967)	 5-FU plus FA (47.5%)	Male: 54% ECOG PS: 0=85%, 1=15% Median age: 63 years (22-82) Male: 54% ECOG PS: 0=85%, 1=15%		adjuvant treatment of patients with stage III colon cancer with efficacy benefits maintained at 5 years and in older patients
Asmis 2011[19]	Phase III	aCRC Second-line ≥65=41% (n=572)	Cetuximab plus best supportive care (n=287) Best supportive care (n=285)	Males=69.6% ≥65 ECOG PS: 0=24.1%, 1=51.5%, 2=24.5% <65 ECOG PS: 0=23.6%, 1=53.7%, 2=22.7% ≥65 tumour site: colon=60.3%, rectum=21.1%, both=18.6% <65 tumour site: colon=56.4%, rectum=24.8%, both=18.8%	Comorbitity, OS	Better PS was associated with improved OS. For patients with good PS, restricting cetuximab use in the setting of significant comorbidity does not appear justified
Allegra 2009[20]	Phase III Multicentre Median follow-up 28.5 months 2004-2006	Stage II/III ≥60=42%	Modified FOLFOX6 with bevacizumab (n=1354) ≥60=41.9% Modified FOLFOX6 (n=1356) ≥60=41.7%	Male=49.8%	Toxicity	Bev with modified FOLFOX6 is well tolerated in the surgical adjuvant setting in these patients. No significant increase in gastrointestinal perforation, haemorrhage, arterial or venous thrombotic events, or death with the addition of bevacizumab to modified FOLFOX6 has been observed
Jackson 2009[21]	Phase III Multicentre United States Follow-up 34 months 2003-2004	mCRC First-line	Period 1: FOLFIRI, mIFL, or CapeIRI (n=430) >70=20%	Median age: 75 years (71-87) Male: 56% >70 PS: 0=49%, 1=51% ≤70 PS: 0=50%, 1=50%	PFS, RR, OS	Irinotecan/fluoropyrimidine combinations are well tolerated in the elderly population, with similar efficacy to that found in non-elderly patients in first-line mCRC

Study	Details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
	Funded by Pfizer Inc, New York Stratified for age at randomisation			>70 tumour site: colon=69%, rectum=31% ≤70 tumour site: colon=68%, rectum=32%		
			Period 2: FOLFIRI plus bevacizumab[b] or mIFL plus bevacizumab[b] (n=117) >70=24%	Median age: 74 (71-84) Males: 76% >70 PS: 0=34%, 1=66% ≤70 PS: 0=60%, 1=39% >70 tumour site: colon=79%, rectum=21% ≤70 tumour site: colon=61%, rectum=39%		
Sastre 2009[22]	Phase III Median follow-up 17.5 months 2002-2004 Funded by Roche and Sanofi Aventis Not stratified for age at randomisation	aCRC First-line ≥70=31.9%	FUOX (5-FU plus oxaliplatin) (n=174)	≥70 median age: 73 years (70-81) <70 median age: 59 years (32-69) ≥70 males: 61.5% <70 males: 60.1% ≥70 KPS: ≥70%=90.8% <70 KPS: ≥70%=89.3%	Efficacy, safety	Elderly patients with mCRC benefit from first-line oxaliplatin–fluoropyrimidine combinations as much as younger patients, without increased toxicity
			XELOX (capecitabine plus oxaliplatin) (n=174)			
Arkenau 2008[23]	Phase III Multicentre Germany, Austria Median follow-up: 17.3 months 2002-2004 Not stratified for age at randomisation	mCRC First-line ≥70=140 (30%)	FUFOX (5-FU plus leucovorin and oxaliplatin) (≥70, n=64)	≥70 ECOG PS: 0-1=86%, 2=14%, <70 ECOG PS: 0-1=94%, 2=6% FUFOX ECOG PS: 0-1=86%, 2=14% CAPOX ECOG PS: 0-1=87%, 2=13%	Toxicity, response	Oxaliplatin combined with 5-FU/leucovorin or capecitabine was generally well tolerated in elderly patients. Elderly patients had similar PFS and overall RRs compared with the population aged <70 years, but the OS was shorter
			CAPOX (capecitabine plus oxaliplatin) (≥70, n=76)			

Study	Details	Population	Intervention (n)	Baseline data	Outcomes	Author conclusions
Figer 2007[24]	Multicentre France, Spain, Israel, Belgium 2000-2002 Stratified for age at randomisation	mCRC First-line >75=37 (6%)	FOLFOX4 (5-FU plus leucovorin and oxaliplatin) until progression (>75, n=20) FOLFOX7 (5-FU plus leucovorin and oxaliplatin) maintenance without oxaliplatin, reintroduction of FOLFOX7 (>75, n=17)	Median age: 77 years (76-80) Male: 59% WHO PS: 0=49%, 1=35%, 2=16% Tumour site: colon=68%, rectum=32%	TTF/DDC, PFS, OS, RR, tolerance	The efficacy of FOLFOX-based treatment was maintained in patients >75 years with both FOLFOX regimens. The oxaliplatin stop-and-go management strategy performed well in this population
Comella 2006[25]	Phase I Italy Not stratified for age at randomisation	mCRC ≥65=61 (44%)	Oxaliplatin plus leucovorin and 5-FU ≥65, n=31 (22%) Bi-weekly oxaliplatin plus leucovorin and 5-FU ≥65, n=31 (22%)	Median age: 63 years (37-79) Male: 59% (≥65) ≥65 PS: 1-2=49% <65 PS: 1-2=43%	Efficacy , tolerability	No significant difference in the occurrence of severe non-haematological toxicity was observed among these two age groups. The low-dose regimen was similarly tolerated in both age groups. The low-dose regimen represents a new treatment option, and also deserves further evaluation in elderly patients

mCRC=metastatic colorectal cancer; aCRC=advanced colorectal cancer; FA=folinic acid; 5-FU=5-fluorouracil; FOLFOX=folinic acid (leucovorin), 5-FU and oxaliplatin; FUFOX=5-FU plus oxaliplatin; FOLFIRI=5-FU, leucovorin, plus irinotecan; FUOX=FU plus oxaliplatin; XELOX=oxaliplatin and capecitabine; mIFL=irinotecan plus bolus 5-FU and leucovorin; TTF=time to failure; DDC=duration of disease control; PFS=progression-free survival; OS=overall survival; RR=response rate; DFS=disease-free survival; RFS=relapse-free survival; ECOG=Eastern Cooperative Oncology Group; AE=adverse event; PS=performance status

[a] CT=fluoropyrimidine-based chemotherapy

[b] Patients were randomised to 1 of the 3 open-label chemotherapy arms: infusional 5-flourouracil (5-FU), leucovorin, and irinotecan (FOLFIRI); bolus 5-FU, leucovorin, and irinotecan (mIFL); or oral capecitabine with irinotecan (CapeIRI), as well as to a double-blind treatment celecoxib or placebo (period 1) using a 3-by-2 factorial design. In April 2004, after US Food and Drug Administration approval of bevacizumab, the trial was amended to compare FOLFIRI and bevacizumab (FOLFIRI+Bev) with mIFL and bevacizumab (mIFL+Bev) using a 2-by-2 factorial design (period 2); the CapeIRI arm was discontinued because of greater toxicity and limited safety data for the addition of bevacizumab to this arm. Following the amendment, patients randomised to FOLFIRI or mIFL during period 1 who were still on study had the option of adding bevacizumab to their current regimen; 16 patients on the FOLFIRI arm and 7 patients on the mIFL arm added bevacizumab to their regimen

7.2 Efficacy evidence

Nine studies[13-19,21-25] reported at least one efficacy outcome of interest. Details can be found in Table 10.

Eight studies[13-18,21-25] reported PFS, time to disease progression (TTP) or time to treatment failure (TTF). The lowest PFS for older patients was 4.3 months,[13] and the highest was 10.4 months.[14-16] Bouche et al[13] reported a significant result for the addition of bevacizumab to chemotherapy versus chemotherapy alone in all patients aged ≥65 (5.5 vs 4.3 months; hazard ratio [HR], 0.71 [95% CI 0.57 to 0.87]; p=0.0011). Sastre et al[22] reported a statistically significant result when comparing TTF for patients aged ≥70 years with those aged <70 (5.5 vs 7.2 months; HR, 1.5 [95% CI 1.2 to 1.9]; p=0.001).

Overall survival was reported in nine studies.[13-19,21-25] For older patients, the lowest OS was 9.8 months[13] and the highest was 21.2 months.[21] Bouche et al[13] reported a statistically significantly longer OS in patients aged <65 for bevacizumab plus chemotherapy versus chemotherapy alone, but the result was not statistically significant for those aged ≥65 years (10.7 vs 9.8 months; HR, 0.83 [95% CI 0.66 to 1.04]; p=0.1056). Arkenau et al[23] reported a statistically significantly longer OS for younger patients compared with older patients regardless of treatment (18.8 vs 14.4 months; HR, 1.37 [95% CI 1.07 to 1.76]; p=0.03).

Six studies[14-16,21-25] reported results for ORR. For older patients, the lowest ORR was 23%[14-16] and the highest was 59.4%.[24] However, none of the results were statistically significant.

Table 10 Efficacy evidence, subgroups of randomised controlled trials

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
Bouche 2012[13] (abstract only)	Oxaliplatin or irinotecan plus bevacizumab	≥65=5.5 <65=5.9	≥65 vs ≥65=0.71 (0.57 to 0.87) p=0.0011 <65 vs <65=0.66 (0.55 to 0.80) p<0.0001	≥65=10.7 <65=11.6	≥65 vs ≥65=0.83 (0.66 to 1.04) p=0.1056 <65 vs <65=0.79 (0.65 to 0.98) p=0.0274	NR	NR
	Oxaliplatin or irinotecan	≥65=4.3 <65=3.9		≥65=9.8 <65=9.9			
Price 2012[14-16]	Capecitabine (C)	≥75=5.6 <75=5.8	≥75 C vs CB=0.65 C vs CBM=0.38 ≥75 vs <75, p=0.24	≥75=13.4 <75=20.0	≥75 vs<75, p=0.48	≥75=28.0 <75=30.9	≥75 vs <75, p=0.08
	Capecitabine plus bevacizumab (CB)	≥75=8.8 <75=8.5		≥75=15.7 <75=20.4		≥75=23.0 <75=41.9	
	Capecitabine plus bevacizumab and mitomycin C (CBM)	≥75=10.4 <75=7.8		≥75=19.9 <75=16.1		≥75=57.0 <75=43.2	
Twelves 2012[17,18]	Capecitabine	5-year DFS: ≥70=58.1% 40-69=59.4% <40=56.0%	Age HR=1.002 (0.995 to 1.009) p=0.6043 C vs 5-FU=0.88 (0.77 to 1.01)	5-year OS: ≥70=68.8% 40-69=70.9% <40=79.1%	Age HR=1.010 (1.001 to 1.019) p=0.0238 C vs 5-FU 0.86 (0.74 to 1.01)	NR	NR
	5-FU	5-year DFS: ≥70 55.8% 40-69=54.5% <40=49.0%		5-year OS: ≥70=65.0% 40-69=68.6% <40=65.6%			
Asmis 2011[19]	BSC and/or cetuximab	NR	NR	NR	1.05 (0.87 to 1.27) p=0.60	NR	NR
Jackson 2009[21]	FOLFIRI or mILF, or capeIRI >70	7.5 (5.9 to 8.6)	0.98 (0.74 to 1.29)	21.2 (14.2 to 23.7)	1.15 (0.87 to 1.51)	47	NR
	FOLFIRI or mILF, or capeIRI ≤70	6.6 (6.0 to 7.1)		19 (17.2 to 23.2)		50	
	FOLFIRI plus bevacizumab,or mIFL plus bevacizumab >70	7.6 (4.3 to 17.4)	1.78 (0.93 to 3.41)	19.4 (11.6 to 26.6)	1.41 (0.83 to 2.41)	NR	NR
	FOLFIRI plus bevacizumab,or mIFL plus bevacizumab ≤70	10.6 (8.5 to 13.8)		25.1 (19.8 to 30.5)			

Study	Intervention		Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
Sastre 2009[22]	≥70 FUOX or XELOX		TTP=8.3 (7.1 to 9.4) TTF=5.5 (4.2 to 6.9)	TTP=1.22 (1.0 to 1.6), p=0.115 TTF=1.5 (1.2 to 1.9), p=0.001	16.8 (13.9 to 19.7)	1.29 (1.0 to 1.7), p=0.74	34.9 (26 to 43.9)	p=0.081
	<70 FUOX or XELOX		TTP=9.6 (8.6 to 10.7) TTF=7.2 (6.4 to 7.9)		20.5 (17.6 to 23.4)		44.7 (38.3 to 51.1)	
Arkenau 2008[23]	≥70 FUFOX		7.9	1.07 (0.86 to 1.34) p=0.54	14.2	≥70 vs <70=1.37 (1.07 to 1.76) p=0.03	54	NR
	≥70 CAPOX		7.6		14.4		46	
	≥70 overall		PFS=7.6 TTF=4.5		14.4		49	
	<70 overall		PFS=7.5 TTF=6.1		18.8		52	
Figer 2007[24]	FOLFOX4 or FOLFOX7	≥75	9	p=0.63	20.7	p=0.57	59.4 (43.4 to 75.6)	NR
		<75	9		20.2		59 (55.1 to 62.9)	
Comella 2006[25]	OXAFAFU	≥65	8.4 (4.9 to 11.9)	NR	19.4 (9.5 to 29.3)	NR	39%	NR
		<65	8.1 (6.9 to 9.3)		18.6 (13.7 to 23.5)		47%	

5-FU=5-fluorouracil; FOLFIRI=5-FU, folinic acid plus irinotecan; FUFOX/FOLFOX/OXAFAFU=5-FU, folinic acid plus oxaliplatin; mILF=irinotecan plus 5-FU; FUOX=5-FU plus oxaliplatin; XELOX/CAPOX=capecitabine plus oxaliplatin; BSC=best supportive care; TTP=time to progression; TTF=time to failure; PFS=progression-free survival; DFS=disease-free survival; ORR=objective response rate; OS=overall survival; HR=hazard ratio; CI=confidence interval; NR=not reported

[a] Values are PFS, unless otherwise stated

7.3 Tolerability evidence

Nine studies[14-25] reported at least one outcome of interest relating to tolerability. Details are presented in Table 11.

Only one study[14-16] reported information regarding dose intensity, with an RDI of 90% across the regimens. One study[20] reported discontinuations, with overall discontinuations due to toxicity (66%) and withdrawal of consent (24%). Dose modifications were reported by four studies,[17,18,21,22,24] and where comparisons across age groups were available, generally the rates of modification or reduction were similar; however, Sastre et al[22] reported that reductions for patients receiving 5-FU plus oxaliplatin (FUOX) were 44.9% in those aged ≥70 and and 26.2% in those aged <70. Figer et al[24] reported an overall rate of 46% for dose reductions due to toxicity for patients treated with FOLFOX4/FOLFOX7 (5-FU plus leucovorin and oxaliplatin).

Adverse events were reported by nine studies,[14-25] and where comparisons between age groups were available the data generally suggest that AE rates were similar for older and younger patients, with a few exceptions. In the capecitabine only arms, Price et al[14-16] reported higher rates of diarrhoea in those aged ≥75 compared with those aged <75. Sastre et al[22] also reported higher rates of diarrhoea in older patients receiving either XELOX/FUOX (capecitabine and oxaliplatin/5-FU plus oxaliplatin) compared with younger patients (25%/32.7% vs 8.1%/20.5%). Asmis et al[19] reported higher rates of fatigue in older patients (38.2% vs 29.8%), and Figer et al[24] reported statistically significantly higher rates of neutropenia for older patients compared with younger patients receiving FOLFOX4/FOLFOX7 (41% vs 24%; p=0.03). Twelves et al[17,18] reported five deaths in the <65 group and two deaths in the ≥65 group.

Table 11 Tolerability evidence, subgroups of randomised controlled trials

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Price 2012[14-16] (abstract only)	Capecitabine ≥75 Median cycles=7	NR	NR	Diarrhoea=19% Rash (hand-foot/PPE)=16% Fatigue=13.5%
	Capecitabine plus bevacizumab ≥75 Median cycles=8/8			Diarrhoea=19% Rash (hand-foot/PPE)=27% Fatigue=12.9%
	Capecitabine <75 Median cycles=8, p=0.19			Diarrhoea=8% Rash (hand-foot/PPE)=16% Fatigue=8.4%
	Capecitabine plus bevacizumab <75 Median cycles=10/10, p=0.14/0.075			Diarrhoea=15% Rash (hand-foot/PPE)=27% Fatigue=10.7%
	Overall median dose intensity >90%			NR
Twelves 2012[17,18a]	NR	NR	Capecitabine Dose modifications: ≥70=65% <70=55%	Diarrhoea: ≥65=13% <65=10%
			5-FU Dose modifications: ≥70=61% <70=50%	Stomatitis: ≥65=18% <65=11% Diarrhoea: ≥65=13% <65=13% Neutropenia: ≥65=27% <65=26%
			NR	Any grade 3-4 toxicity ≥65=19.7% <65=15.1% (first 21 days) for 5-FU only Treatment related deaths: ≥65=2 deaths <65=5 deaths
Asmis 2011[19]	≥65 BSC and/or cetuximab Median dose=2202 mg/m² (395.8-15216)	NR	NR	Fatigue=38.2% Non-neutropenic infection=10.9% Other pain=10.9% Dyspnoea=24.5% Rash=12.7%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
	<65 BSC and/or cetuximab Median dose=2155 mg/m² (390.8-10331)			Fatigue=29.8% Non-neutropenic infection=14.0% Other pain=17.4% Dyspnoea=11.2% Rash=11.2% Abdominal pain=16.2%
Allegra 2009[20]	NR	Overall: Discontinuation: toxicity=66.7%, withdrawal of consent=24%	NR	FOLFOX6 Any grade ≥3=70.0% Any grade 3-5=15.2% Neutropenia=32.6% Diarrhoea=9.7%
				FOLFOX6+ bevacizumab Any grade ≥3=77.0% Any grade 3-5=15.0% Neutropenia=29.4% Diarrhoea=11.1%
				FOLFOX6+/- bevacizumab ≥60 Any grade ≥3=81% Grade 3 neutropenia=44.2% Grade 3 fatigue=15.2% Grade 3 diarrhoea=16.4% Grade 3 dehydration=10.9% Grade 4 neutropenia=13%
				FOLFOX6+/- bevacizumab <60 Any grade ≥3=73% Grade 3 neutropenia=28.8% Grade 3 fatigue=6.9% Grade 3 diarrhoea=9.5% Grade 3 dehydration=3.4% Grade 4 neutropenia=6%
Jackson 2009[21]	NR	NR	>70 Reduction=13% Delay=38% Both=20% ≤70 Reduction=17%	>70 FOLFIRI Leukopenia=25% Neutropenia=54% Abdominal pain=11% Diarrhoea=11% Vomiting=11% DVT=11%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
			Delay=32% Both=16%	≤70 FOLFIRI Leukopenia=18% Neutropenia=40% Diarrhoea=15% Fatigue=13% DVT=10%
				>70 mIFL Febrile neutropenia=12% Leukopenia=27% Neutropenia=46% Diarrhoea=23% Asthenia=12%
				≤70 mIFL Febrile neutropenia=13% Leukopenia=22% Neutropenia=40% Diarrhoea=18% Fatigue=11%
			NR	>70 FOLFIRI + bevacizumab Febrile neutropenia=14% Leukopenia=36% Neutropenia=71% Nausea=14% Vomiting=14%
				≤70 FOLFIRI + bevacizumab Leukopenia=26% Neutropenia=48% Abdominal pain=12% Diarrhoea=12% Nausea=10% Vomiting=10%
				>70 mIFL + bevacizumab Leukopenia=13% Neutropenia=40% Diarrhoea=13%
				≤70 mIFL + bevacizumab Leukopenia=14% Neutropenia=25% Diarrhoea=11%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Sastre 2009[22]	XELOX ≥70 Median cycles=6	NR	Capecitabine reduction=18.3%, Oxaliplatin reduction=16.7% Delay=55.0%	Neutropenia=11.7% Parethesia=20.0% Asthenia=10% Diarrhoea=25.0%
	XELOX <70 Median cycles=7		Capecitabine reduction=21.6% Oxaliplatin reduction=21.6% Delay=59.6%	Neutopenia=4.5% Parethesia=17.1% Asthenia=13.5% Diarrhoea=8.1%
	FUOX ≥70 Median cycles=3		5-FU reduction=44.9% Oxaliplatin reduction=30.6% Delay=75.5%	Neutropenia=6.1% Paresthesia=20.4% Diarrhoea=32.7%
	FUOX <70 Median cycles=4		5-FU reduction=26.2% Oxaliplatin reduction=23.0% Delay=76.2%	Neutropenia=12.3% Paresthesia=15.6% Diarrhoea=20.5%
Arkenau 2008[23]	NR	NR	NR	FUFOX or CAPOX ≥70 Diarrhoea=21% Neuropathy=21%
				FUFOX or CAPOX <70 Diarrhoea=12% Neuropathy=30%
Figer 2007[24]	FOLFOX4 and FOLFOX7 Median cycles per patient=12 (2-51)	NR	Dose reduction=17 (46%), due to toxicity	>75 Any grade 3-4=65% Neutropenia=41% Neurotoxicity=22%
				≤75 Any grade 3-4=48%, p=0.06 Neutropenia=24%, p=0.03 Neurotoxicity=11%, p=0.06
Comella 2006[25]	Oxaliplatin plus L-leucovorin and 5-fluorouracil Median cycles=9 (1-12) over 18 (2-39) weeks	NR	NR	≥65 High dose Neutropenia=29% Neuropathy=13% Diarrhoea=19%
				<65 High dose Neutropenia=40% Neuropathy=10
				≥65 Low dose Neutropenia=23% Diarrhoea=13%
				<65 Low dose Neutropenia=16%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
				Diarrhoea=10%

DVT=deep vein thrombosis; PPE=palmar-plantar erythrodysesthesia; 5-FU=5-fluorouracil; FOLFOX/FUFOX=5-FU plus folinic acid and oxaliplatin; FUOX=5-FU plus oxaliplatin; FOLFIRI=5-FU, leucovorin, plus irinotecan; CAPOX=capeciteabine plus oxaliplatin; mIFL=irinotecan plus bolus 5-FU and leucovorin; XELOX=oxaliplatin plus capecitabine; BSC=best supportive care; NR=not reported

[a] The age cut-off was reported differently in each published paper

7.4 Comprehensive geriatric assessment and quality of life

None of the included studies reported QoL or CGA outcomes.

7.5 Discussion

Ten studies[13-25] that reported results from subgroups of RCTs were included in the review. The majority of the studies derived data from phase III RCTs and enrolled patients with aCRC/mCRC, and where stated, most studies focussed on first-line treatment.

Efficacy outcomes were well reported, and the general trend for PFS, OS and ORR was that older patients achieved similar results to younger patients. There were statistically significant results reported. One study[13] reported a significant PFS result for the addition of bevacizumab to chemotherapy versus chemotherapy alone in patients aged ≥65 (5.5 vs 4.3 months; HR, 0.71 [95% CI 0.57 to 0.87]; p=0.0011). Another study[22] reported a statistically significant result when comparing TTF for patients aged ≥70 years with those aged <70 (5.5 vs 7.2 months; HR, 1.5 [95% CI 1.2 to 1.9]; p=0.001). One study[23] reported a statistically significantly longer OS for younger patients compared with older patients(18.8 vs 14.4 months; HR, 1.37 [95% CI 1.07 to 1.76]; p=0.03).

There was some evidence that older patients experienced higher rates of AEs compared with younger patients; however, older patients also appeared to tolerate treatment well.

None of the studies presented data relating to the use of CGA tools or QoL measures.

8 POOLED ANALYSES

Seven studies[26-35] that used aggregated subgroup data from RCTs were included in the review. Details of the study characteristics are presented in Table 12.

8.1 Study characteristics

Where reported, data were derived from phase II/III RCTs.[28,29,31-34] Four studies[28-30,32-34] were international. The enrolment periods of the studies covered a wide period of time, with the earliest study beginning in 1984[35] and the latest study finishing in 2006.[26,27] Four studies[28-33] reported that they were funded by pharmaceutical companies.

Five studies[26-33] focussed on patients with mCRC, one study[35] focussed on patients with aCRC and one study[34] did not report the stage of disease. Four studies[26,27,30-34] investigated first-line treatment, two studies[28,29,34] investigated both first- and second-line treatment, and one study[35] did not report specific information. Five studies[26,27,30,32-35] defined 'older' as ≥70 years and two studies [28,29,31] used ≥65 years. The proportion of older patients in each study varied from 16.4%[34] to 43%.[31] Where reported, studies included higher proportions of PS 0-1 patients.

Table 12 Study characteristics, pooled analyses

Study	Study details	Population	Intervention (n)	Baseline data	Purpose	Author conclusions
Venderbosch 2012[26,27]	Analysis of selected arms from two RCTs Multicentre The Netherlands 2003-2004 and 2005-2006	mCRC First-line ≥70=26% ≥70=33%	Capecitabine (n=401) >75=9% 70-75=16% <70=74%	PS: 0=64.1%, 1=31.4%, 2=4.5%	A retrospective analysis of the efficacy, drug administration, tolerability, and global QoL of capecitabine, capecitabine irinotecan (CAIRO study) and capecitabine oxaliplatin bevacizumab (CAIRO2 study) in elderly (70-75 years and 75 years) compared with younger patients (<70 years) with mCRC	We did not observe significant differences in survival outcomes between elderly and younger mCRC patients with three different first-line systemic treatment regimens. Our data suggest that initial dose reduction of capecitabine monotherapy may be indicated in elderly patients
			CAPIRI (n=402) >75=45% 70-75=19% <70=67%	PS: 0=60.7%, 1=35.3%, 2=4.0%		
			CAPOX plus bevacizumab (n=368)	Male: 56%		
Cassidy 2010[28,29]	Analysis of four phase II and III trials Multicentre UK, USA, Switzerland Funded by Roche	mCRC First- and second-line ≥65=38% ≥70=24%	Fluoropyrimidine-based chemotherapy [FOLFOX4, XELOX or I-FL] with bevacizumab (overall n=3006)	Median age: 61 years (18-89) <65=56 (18-64); ≥65=72 (65-89); ≥70=74 (70-89) Males: 59% <65=58%; ≥65=62%; ≥70=63%	The present retrospective analysis was undertaken to compare the efficacy and safety of bevacizumab plus chemotherapy in older vs younger patients with mCRC who participated in four randomised phase II and III trials that included over 1,100 patients aged >65 years	In medically fit older patients, bevacizumab provides similar PFS and OS benefits as younger patients
			Fluoropyrimidine-based chemotherapy [FOLFOX4, XELOX or IFL] without bevacizumab	Median age: 61 years (18-90) <65=54 (18-64); ≥65=71 (65-90); ≥70=74 (70-90) Males: 58% <65=56%; ≥65=60%; ≥70=57%		
Folprecht 2010[30] (abstract only)	Analysis of CRYSTAL and OPUS trials Germany, Belgium, France Funded by Merck Serono and Pfizer	mCRC First-line ≥70=17%	FOLFIRI and FOLFOX +/- cetuximab (n=845)	NR	To explore the effect of age on efficacy and safety of cetuximab and chemotherapy	With a cut-off of 70 years, no major interference between age and efficacy of cetuximab in combination with standard chemotherapy or on the differences for toxicity was shown. Further analysis including additional safety and efficacy data are

Study	Study details	Population	Intervention (n)	Baseline data	Purpose	Author conclusions
						ongoing
Kabbinavar 2009[31]	Analysis of two Phase III trials Multicentre United States Funded by Genentech Inc. Sanofi-Aventis	mCRC First-line ≥65=43% >70=27%	FOLFIRI or 5-FU and leucovorin plus bevacizumab (n=218)	Overall median age:72 years (65-90) Overall males=59.5% ECOG PS: 0=47.2%, 1=49.5%, 2=3.2%	To provide more statistical power to assess risk/benefit in older patients, we examined the clinical benefit of bevacizumab plus fluorouracil-based chemotherapy in first-line mCRC treatment in patients aged ≥65 years, using data pooled from two placebo-controlled studies	Analysis of pooled patient cohorts age ≥65 years from two similar trials in mCRC indicates that adding bevacizumab to fluorouracil-based chemotherapy improved OS and PFS, similar to the benefits in younger patients. Also, the risks of treatment do not seem to exceed those in younger patients with mCRC
			FOLFIRI or 5-FU and leucovorin plus placebo (n=221)	ECOG PS: 0=46.2%, 1=51.6%, 2=2.3%		
Folprecht 2008[32,33]	Four phase III trials Multicentre Germany, UK, USA, France and Belgium 1996-2003 Funded by Pfizer	mCRC First-line ≥70=22.3%	≥70 I-FU (n=220) FU/FA (n=379)	Overall males: 69.5% PS: 0=41.4%, 1=49.9%, 2=9.8% Tumour site: colon=29.9%, rectum=69.3%, both=0.8%	To extend earlier observations and to consider the relative performance of FU/FA/irinotecan combinations compared with FU/FA alone in both elderly and younger patients	Patients older than 70 years of age who were selected for inclusion in phase III trials derived similar benefits as younger patients from irinotecan-containing chemotherapy, and the risk of toxicity was similar
			<70 I-FU (n=777) FU/FA (n=1315)	PS: 0=46.0%, 1=45.4%, 2=8.5% Tumour site: colon=30.4%, rectum=63.9%, both=0.8%		
Goldberg 2006[34]	Phase II/III Analysis of 4 trials International 1995-2002	First- and second-line ≥70=16.4%	FOLFOX4 or 5-FU and leucovorin or FOLFIRI (n=3743)	Tumour site: colon=100%	This analysis compares the safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly (FOLFOX4) in patients aged <70 and ≥70 years	FOLFOX4 maintains its efficacy and safety ratio in selected elderly patients with CRC. Its judicious use should be considered without regard to patient age, although scant data are available among patients older than 80 years

Study	Study details	Population	Intervention (n)	Baseline data	Purpose	Author conclusions
D'Andre 2005[35]	Analysis of four trials 1984-1997 Funded by Grant CA 25224	aCRC >70=28% <55=21% 56-65=31% 66-80=20%	Four trials comparing 5-FU-based regimens NCCTG 834652 (n=706) NCCTG 884651 (n=372) NCCTG 894652 (n=952) NCCTG 954651 (n=77)	Males:42% ECOG PS: 0=36%, 1=49%, 2=14%, 3=2%	Our primary goal was to compare the toxicity patterns for older and younger patients. We also compared the dose intensity, response rate, TTP, and OS of older and younger patients	Age alone should not be used to determine whether older patients are treated, because PS is predictive of dose intensity, response rate, TTP, and OS

RCT=randomised controlled trial; mCRC=metastatic colorectal cancer; aCRC=advanced colorectal cancer; 5-FU=5-fluorouracil; FOLFOX=folinic acid (leucovorin), 5-FU plus oxaliplatin; FOLFIRI=Irinotecan plus 5-FU; XELOX=oxaliplatin plus capecitabine; I-FL=irinotecan plus leucovorin; I-FU=irinotecan plus 5-FU; FU/FA=5-FU plus leucovorin; CAPIRI=capecitabine plus irinotecan; PFS=progression-free survival; OS=overall survival; ECOG=Eastern Cooperative Oncology Group; PS=performance status; QoL=quality of life; NR=not reported

8.2 Efficacy evidence

Seven studies[26-35] presented one or more outcomes of interest. Efficacy outcomes are presented in Table 13.

Six studies[26-35] presented outcomes for PFS/TTP. The lowest reported PFS for older patients was 6.1 months[26,27] and the highest was 13.5[26,27] months. For younger patients the lowest PFS was 5.5 months[26,27] and the highest was 10.6 months.[26,27]

All studies[26-35] reported OS. For older patients, this ranged from 10.4 months[35] to 23.3 months,[30] and for younger patients, OS ranged from 12 months[35] to 23.6 months.[30] Where OS was compared between age groups, no statistically significant results were reported.

Four studies[26,27,31-33,35] reported data for ORR. Older patients achieved an ORR ranging from 25.5%[31] to 50.5%,[32,33] and for younger patients ORR ranged from 16%[26,27] to 48%.[26,27]

Table 13 Efficacy evidence, pooled analyses

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
Venderbosch 2012[26,27]	>75 Capecitabine	7.8 (5.9 to 9.3)	>75=0.76 (0.54 to 1.07)	18.2 (11.5 to 22.3)	>75=1.05 (0.74 to 1.49)	31	p=0.025
	70-75 Capecitabine	6.1 (4.5 to 7.3)	70-75=0.87 (0.66 to 1.13)	17.5 (12.6 to 21.7)	70 to 75=0.87 (0.66 to 1.15)	27	
	<70 Capecitabine	5.5 (4.6 to 6.1)	p=0.198	16.0 (14.0 to 17.7)	p=0.576	16	
	>75 CAPIRI	7.2 (4.5 to 10.2)	>75=1.10 (0.68 to 1.77)	17.1 (7.3 to 22.3)	>75=1.16 (0.70 to 1.93)	38	p=0.818
	70-75 CAPIRI	7.2 (6.3 to 8.4)	70-75=0.95 (0.74 to 1.23)	20.0 (12.7 to 22.4)	70 to 75=0.88 (0.76 to 1.15)	32	
	<70 CAPIRI	7.8 (6.9 to 8.3)	p=0.843	16.8 (14.9 to 18.3)	p=0.542	36	
	>75 CAPOX + bevacizumab	13.5 (4.7 to 16.8)	>75=1.15 (0.52 to 2.51)	13.1 (6.1 to 25.4)	>75=1.36 (0.64 to 2.88)	38	p=0.335
	70-75 CAPOX + bevacizumab	9.6 (7.5 to 12.1)	70-75=0.94 (0.69 to 1.26)	17.6 (13.1 to 25.8)	70 to 75=1.15(0.84 to 1.56)	39	
	<70 CAPOX + bevacizumab	10.6 (9.1 to 11.7)	p=0.908	20.3 (17.9 to 24.3)	p=0.063	48	
Cassidy 2010[28,29]	<65 5-FU-based chemotherapy + bevacizumab	9.5	<65=0.59 (0.52 to 0.66)	19.9	<65=0.77 (0.69 to 0.86)	NR	NR
	≥65 5-FU-based chemotherapy + bevacizumab	9.3	≥65=0.58 (0.49 to 0.68)	17.9	≥65=0.85 (0.74 to 0.97)		
	≥70 5-FU-based chemotherapy + bevacizumab	9.2	≥70=0.54 (0.44 to 0.66)	17.4	≥70=0.79 (0.66 to 0.93)		
	<65 5-FU-based chemotherapy without bevacizumab	6.7		16.5	<65, with vs without Bevacizumab, p<0.0001		
	≥65 5-FU-based chemotherapy without bevacizumab	6.9		15.0	≥65, with vs without Bevacizumab, p=0.015		
	≥70 5-FU-based chemotherapy	6.4		14.1	≥70, with vs without Bevacizumab, p=0.005		

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
	without bevacizumab						
Folprecht 2010[30]	≥70 FOLFOX/FOLFIRI + cetuximab	8.9 (7.2 to 16.1)	NR	23.3 (16.8 to 25.7)	NR	NR	NR
	<70 FOLFOX/FOLFIRI + cetuximab	10 (9.0 to 11.5)		23.6 (20.7 to 26.8)			
	≥70 FOLFOX/FOLFIRI	7.2 (6.0 to 9.3)		15.1 (12.6 to 18.8)			
	<70 FOLFOX/FOLFIRI	7.7 (7.4 to 8.9)		20.2 (18.6 to 22)			
Kabbinavar 2009[31]	5-FU-based chemotherapy + Bevacizumab ≥65	9.2 (8.3 to 11.6)	Bevacizumab vs placebo: ≥65=0.52 (0.40 to 0.67), p<0.0001 <65=0.57 (0.46 to 0.70), p<0.0001 >70=0.51 (0.37 to 0.70), p<0.0001	19.3 (16.3 to 22.5)	Bevacizumab vs placebo: ≥65=0.70 (0.55 to 0.90), p=0.006 <65=0.69 (0.55 to 0.88), p=0.002 >70=0.69 (0.51 to 0.93), p=0.015	34.4	Bevacizumab vs placebo: ≥65, p=0.220 <65, p=0.0007
	<65 5-FU-based chemotherapy + bevacizumab	10.5 (9.0 to 10.9)		19.9 (17.4 to 22.8)		45.8	
	>70 5-FU-based chemotherapy + bevacizumab	9.2		18.7		30.9	
	≥65 5-FU-based chemotherapy + placebo	6.2 (5.5 to 8.0)		14.3 (11.9 to 16.9)		29.0	
	<65 5-FU-based chemotherapy + placebo	5.8 (5.5 to 7.1)		16.1 (14.7 to 17.5)		32.2	
	>70 5-FU-based chemotherapy + placebo	6.2		12.6		25.5	
Folprecht 2008[32,33]	≥70 FU + FA	7 (6.2 to 7.9)	FU + FA vs I-FU: ≥70=0.75 (0.61 to 0.9), p<0.0001 <70=0.77 (0.7 to 0.85), p=0.0026 ≥75=0.80 (0.57 to 1.13), p=0.21	14.2 (12.7 to 15.7)	FU + FA vs I-FU: ≥70=0.87 (0.72 to 1.05), p=0.15 <70=0.83 (0.75 to 0.92), p=0.0003 ≥75=1.11 (0.80 to 1.56), p=0.53	30.3 (25.5 to 35.5)	FU + FA vs I-FU: ≥70, p<0.0001 <70, p<0.0001 ≥75, p=0.006
	<70 FU + FA	6.3 (5.9 to 6.7)		14.7 (13.9 to 15.6)		29 (26.4 to 31.6)	
	≥75 FU + FA	7.7 (6.1 to 9.3)		14.2 (10.8 to 17.7)		26.4 (18.3 to 35.9)	
	≥70 I-FU	9.2 (8.5 to 9.9)		17.6 (15.5 to 19.7)		50.5 (43.5 to 57.5)	
	<70 I-FU	8.2 (7.7 to 8.7)		17.1 (15.9 to 18.3)		46.6 (42.9 to 50.2)	
	≥75 I-FU	9.2 (8 to 10.4)		14.5 (11.1 to 17.9)		48.3 (38.3 to 64.8)	

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI) p value	Median OS (95% CI) Months	Hazard ratio (95% CI) p value	ORR % (95% CI)	Hazard ratio (95% CI) p value
Goldberg 2006[34]	FOLFOX4	NR	≥70 vs <70 PFS/DFS, p=0.7 FOLFOX vs control: ≥70=0.65 (0.52 to 0.81) <70=0.7 (0.63 to 0.77) ≥70 vs <70 treatment interaction, p=0.42	NR	FOLFOX vs control: ≥70=0.82 (0.63 to 1.06) <70=0.77 (0.67 to 0.88) ≥70 vs <70 treatment interaction, p=0.79	NR	NR
D'Andre 2005[35]	<55 5-FU regimens	TTP: 5.3	p=0.25	12.0	p=0.42	30	p=0.90
	56-65 5-FU regimens	NR		NR		27	
	66-70 5-FU regimens	NR		NR		29	
	>70 5-FU regimens	TTP: 6.5		10.4		27	

NR=not reported; CAPIRI=capecitabine plus irinotecan; CAPOX=capecitabine plus oxaliplatin; FOLFOX=folinic acid (leucovorin), 5-FU plus oxaliplatin; FOLFIRI=Irinotecan plus 5-FU; PFS=progression-free survival; TTP=time to progression; 5-FU=5-fluorouracil; I-FU=irinotecan plus fluorouracil; FU + FA=fluorouracil and folinic acid

[a] Values are PFS, unless otherwise stated

8.3 Tolerability evidence

All seven included studies[26-35] presented data for at least one outcome of interest. Details are presented in Table 14.

One study[35] presented data regarding the proportion of patients receiving three and six cycles, and found that older patients (>70) received fewer cycles of treatment than younger patients (three cycles p=0.025; six cycles p=0.014). Two studies[26,27,31] reported data for discontinuations, and none of the studies reported data on dose reductions and/or modifications. All studies[26-35] reported rates of grade 3-4 AEs. Not all studies reported the same AEs, and comparisons across studies were difficult to make.

Cassidy et al[28,29] investigated the use of chemotherapy with or without bevacizumab, and across arms and age groups, the figures for arterial thrombotic events, and deaths due to AEs were similar. Kabbinavar et al[31] and Folprecht et al[30] both reported higher rates of diarrhoea in older patients compared with younger patients.

Table 14 Tolerability evidence, pooled analyses

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Venderbosch 2012[26,27]	NR	Capecitabine: >75 Progression=47% Toxicity=20%	NR	51%
		70-75 Progression=72% Toxicity=3%		48%
		<70 Progression=74% Toxicity=10%		28%
	NR	Capecitabine plus irinotecan: >75 Progression=35% Toxicity=30%	NR	50%
		70-75 Progression=33% Toxicity=28%		50%
		<70 Progression=45% Toxicity=15%		49%
	NR	Oxaliplatin plus bevacizumab: >75 Progression=47% Toxicity=35%	NR	82%
		70-75 Progression=38% Toxicity=40%		72%
		<70 Progression=61% Toxicity=19%		75%
Cassidy 2010[28,29]	NR	NR	NR	Chemotherapy plus bevacizumab: ≥65 Arterial thrombotic events=5.7% Deaths due to AEs=10%
				<60 Deaths due to AEs=7%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
				≥70 Arterial thrombotic events=6.7% Deaths due to AEs=6%
	NR	NR	NR	Chemotherapy alone: ≥65 Arterial thrombotic events=2.5% Deaths due to AEs=6%
				<65 Deaths due to AEs=5%
				≥70 Arterial thrombotic events=3.2% Deaths due to AEs=3%
Folprecht 2010[30] (abstract only)	NR	NR	NR	FOLFOX plus cetuximab: ≥70 Neutropenia=33.3% Diarrhoea=23.1%
				<70 Neutropenia=31.2% Diarrhoea=12.8%
	NR	NR	NR	FOLFOX alone: ≥70 Neutropenia=35.8% Diarrhoea=14.9% Skin toxicity=23.1%
				<70 Neutropenia=23.7%
Kabbinavar 2009[31]	NR	≥65 Bevacizumab chemotherapy Discontinuation due to AEs=14.8%	NR	Any grade 3-4 AE=90% Diarrhoea=38.6% Leukopenia=30% Hypertension=13.8%
	NR	<65 Placebo plus chemotherapy Discontinuation due to AEs=12%	NR	Any grade 3-4 AE=75.6% Diarrhoea=33.2% Leukopenia=23.5%
Folprecht 2008[32,33]	NR	NR	NR	I-FU: ≥70 Leukopenia=18.5% Neutropenia=29.7% Diarrhoea=23.4% Nausea=10.8%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
				<70 Leukopenia=16.9% Neutropenia=28.9% Diarrhoea=20.5% Nausea=11.3%
				FU + FA: ≥70 Neutropenia=19.9% Diarrhoea=12.6%
				FU + FA<70 Neutropenia=16.1% Diarrhoea=11.4%
Goldberg 2006[34]	NR	NR	NR	FOLFOX4: ≥70 Any grade ≥3 toxicity=67% Neutropenia=49% Neurotoxicity=12% Diarrhoea=13%
				<70 Any grade ≥3 toxicity=63%, p=0.15 Neutropenia=43%, p=0.04 Neurotoxicity=14%, p=0.37 Diarrhoea=11%, p=0.38
D'Andre 2005[35]	5-FU-based chemotherapy ≤55 3 cycles=73% 6 cycles=40% 5-FU-based chemotherapy 56-65 3 cycles=73% 6 cycles=45%	NR	NR	<65 Any grade ≥3=46% Diarrhoea=16% Leukopenia=14% Stomatitis=13%
	5-FU-based chemotherapy 66-70 3 cycles=69% 6 cycles=46%			66-70 Any grade ≥3=53% Diarrhoea=23% Leukopenia=18 Stomatitis=18%
	5-FU-based chemotherapy >70 3 cycles=66%, p=0.025 6 cycles=37%, p=0.014			>70 Any grade ≥3=53%, p=0.01 Diarrhoea=21%, p=0.01 Leukopenia=17%, p=0.23 Stomatitis=17%, p=0.03

FOLFOX=5-fluorouracil, folinic acid plus oxaliplatin; I-FU=irinotecan plus fluorouracil; FU + FA=fluorouracil plus folinic acid; AE=adverse event; NR=not reported

8.4 Comprehensive geriatric assessment and quality of life

None of the studies presented data on CGA or QoL outcomes.

8.5 Discussion

Seven pooled analyses[26-35] were included in the review. Studies were conducted between 1984 and 2006 and, where stated, focussed on aCRC or mCRC. 'Older' was defined as ≥65 or ≥70.

Efficacy outcomes were well reported. Reported PFS rates for older patients varied from 6.1 months[26,27] to 13.5 months[26,27] and were generally comparable to PFS rates for younger patients. For older patients, OS ranged from 10.4 months[35] to 23.3 months,[30] and no statistically significant results were reported for comparisons across age groups. Older patients achieved ORRs that ranged from from 25.5%[31] to 50.5%,[32,33] and rates were similar to those of younger patients.

Although all included studies[26-35] presented data for at least one outcome of interest, data were lacking for many outcomes and therefore synthesis and comparisons were difficult.

None of the studies reported data for CGA or QoL outcomes.

9 SINGLE COHORTS

In total, 49 cohort studies[36-98] met the inclusion criteria and were included in the review. Details of the study characteristics reported for each study are presented in Table 15. Data were available in abstract only format for 11 studies.[39,40,42,58,65,73,74,80,82,83,88,94,98] Data were poorly reported in most of the studies.

9.1 Study characteristics

Two studies[46,61,86] were phase III, 25 studies[37,38,40,42-45,47-55,57,59,60,68-72,76,77,80,82-85,95,97,98] were phase II and 22 studies[36,39,41,56,58,62,65-67,73,74,78,79,81,87-94,96] did not report the phase. Nine studies[39,56,62,66,67,73,74,86,94,95] recruited more than 100 patients. The majority of studies were conducted in European centres, four studies[39,40,47,88] did not report the country, and 11 studies were conducted in Asia,[36,41,42,44,58,87] the US,[57,62,65,68] and Egypt.[97] Where reported, 26 studies[39,40,44,46,52-56,58,60-62,65,67,68,71-74,76-78,80,81,86,94-97] were multicentre, and eight studies[36-38,42,43,66,87,91,92] were single centre. Studies were conducted between 1997 and 2011. The majority of studies did not report the source of funding. Nine studies[47,57,62,67,68,76,77,81,95] were supported by pharmaceutical companies, and six studies[41,44,49,50,57,66,96] were supported by research grants.

Where explicitly stated, the majority of studies focussed on mCRC. Where reported, studies were first-line, with the exception of five studies.[53-55,67,94,96,98] The most frequent definition of 'older' (cut-off age for study entry) was ≥70 years of age; however, a small proportion of studies used ≥65 or ≥75 years. The smallest study recruited 16 older patients,[57] and the largest study recruited 2032 patients.[65]

Table 15 Study characteristics, single cohorts

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Rosati 2013[53-55]	Phase II Multicentre Italy Follow-up 17 months 2010-2011	mCRC First-line/maintenance after progression ≥70 (≥75=43%)	XELOX plus bevacizumab followed by bevacizumab alone (n=44)	Median age=74 years (70-83) Males=52% ECOG PS: 0=73%, 1=27% Tumour site: colon=77%, rectum=23%	Safety and response rates	The combination of XELOX and bevacizumab is effective and has a manageable tolerability profile when administered to elderly patients with advanced CRC. Maintenance therapy with single-agent bevacizumab may be considered to extend PFS in this setting of patients
Abdelwahab 2012[97]	Phase II Multicentre Egypt 2008-2011	mCRC First-line ≥65	Cetuximab and Irinotecan (n=49)	Median age: 69 years (65-77) Males=76% KPS: 100=14%, 90=41%, 80=45% Tumour site: colon=76%, rectum=24%	Primary: RR Secondary: toxicity	Cetuximab combined with irinotecan when administered bi-weekly is safe and effective for treatment of pretreated elderly patients with mCRC
Benavides 2012[95]	Phase II Multicentre Spain Follow-up 14 months 2003-2006 Funded by Sanofi-Aventis	mCRC First-line ≥72	Oxaliplatin plus 5-FU (n=129)	Median age: 76 years (72-85) Males: 63% ECOG PS: 0=42%, 1=53%, 2=5% Tumour site: colon=65%, rectum=34%, both=1%	Primary: ORR, survival Secondary: treatment compliance, safety	To our knowledge, this is the largest phase II prospective study in elderly patients with mCRC. The observed efficacy and safety of this schedule compared favourably with those reported in this population, including regimens with monoclonal antibodies
Berretta 2012[90]	Italy Follow-up 27 months 1998-2009	mCRC Dukes stage: A-B=20%, Stage C=45.3%, Stage D=34.7% ≥65	FOLFOX4 FOLFOX2 (n=75)	Median age=71 years (65-75) Males=68% PS:0=57.3%, 1=38.7%, ≥2=4% Tumour site: colon=98.7%, rectum=1.3%	Primary: feasibility, safety Secondary: treatment response, toxicity, survival	Oxaliplatin-based chemotherapy maintains its efficacy, and safety in elderly patients with mCRC and good PS. This regimen should be considered in the treatment of this particular cohort

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Chang 2012[87]	Single centre Korea Follow-up 45 months 2005-2009	High risk stage II: 27 (32.9%), stage III=55 (67.1%) First-line ≥70 (≥75=50%)	Capecitabine (n=82)	Median age: 74.5 years (70-90) ECOG PS: 0=4.9%, 1=63.4% 2=31.7% Tumour site: colon=100%	Dose intensity, toxicity,QoL	A tailored-dose escalation strategy was feasible in elderly colorectal cancer patients receiving adjuvant capecitabine chemotherapy. Decreased renal function and an increased number of comorbidities were independently predictive of reduced administration of the capecitabine dose
Jehn 2012[67]	Multicentre Germany 2005-2007 Funded by Merck Serono	mCRC 1-4 previous lines of therapy >65=49.7%	>65 Cetuximab-based chemotherapy (Overall n=614)	Median age: 71 years (66-89) Males: 64% ECOG PS: 0=17%, 1=59%, 2=19%, 3=4% Tumour site:colon=60%, rectum=40%	Efficacy, safety	This NIS reports one of the largest mCRC collectives >65 years and reduced performance status. Cetuximab has a similar efficacy and safety profile for patients aged >65 and ≤65 years
			≤65 Cetuximab-based chemotherapy	Median age: 59 years (23-65) Males: 66% ECOG PS: 0=19%, 1=61%, 2=16%, 3=4% Tumour site: colon=60%, rectum=40%		
Sastre 2012[47,48]	Phase II Follow-up 14.4 months 2006-2007 Merck	mCRC First-line ≥70	Cetuximab plus capecitabine (n=66)	Median age: 77 years (70-86) Males: 57.6% KPS: 70%=15%, 80%=37.9%, 90%=28.8%, 100%=30.3%, NA=1.5%	Primary: ORR Secondary: safety, PFS, OS	Cetuximab plus capecitabine at a dose of 1,000 mg/m^2 every 12 hours may be an alternative to more aggressive regimens in elderly patients with advanced wild-type KRAS CRC
Scartozzi 2012[45]	Phase II Italy	mCRC Genetic markers: TS,	5-FU (n=1)	Males=83%	Primary: RR Secondary: toxicity	Prospective selection of chemotherapy based on TS,

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	2006-2009	ERCC1, DPD, UGT1A1 First-line ≥70	5-FU plus irinotecan (n=12) Irinotecan plus oxaliplatin (n=11)	ECOG PS:0-1=75%, 2=25% Tumour site: colon=67%, rectum=33%		DPD, ERCC-1 and UGT1A1 expression in elderly mCRC patients failed to confirm previous results. A more accurate validation of retrospective findings is warranted before these molecular markers can be used for treatment selection in the clinical practice
Bennouna 2011[94] (abstract only)	Multicentre France Follow-up 6 months	mCRC All lines of treatment ≥70=64% (>75=18%)	Various chemotherapy plus bevacizumab (n=515)	ECOG PS: ≥2=7.4% (≥75=14.3%)	Safety, PFS, OS	Results of this prospective cohort study suggest that the efficacy of first-line treatment with bevacizumab and chemotherapy is independent of age and is tolerable in elderly patients with mCRC
Berretta 2011[89]	Italy Median follow-up 14.5 months 2002-2008	mCRC Duke's stage: A/B=2.8%, C=33.3%, D=63.9% First-line ≥67	FOLFOX4 (n=36)	Median age=72 years (67-82) Males=61.1% ECOG PS: 0=52.8%, 1=41.7%, ≥2=5.5% Tumour site: colon=75%	Toxicity, efficacy	Our data show that the FOLFOX4-regimen maintains its activity and feasibility also in the fit elderly population, and PS and geriatric assessment are surely better criteria than only ‘‘anagraphic’’ age evaluation to predict the efficacy and toxicity of chemotherapy
Carreca 2011[88] (abstract only)	2009	≥70	Capcitabine and oxaliplatin plus bevacizumab (n=75)	Median age: 76 years (70-82) Male: 50%	Primary: toxicity, QoL Secondary: CRR	This schedule is active and safe because it improves tolerability without decrease of efficacy in these patients
Di Bartolomeo 2011[80] (abstract only)	Phase II Multicentre Italy	mCRC First-line ≥70	TEGAFOX-E (n=28)	NR	Response, PFS	TEGAFOX-E combination displayed promising efficacy in patients with both wild-type KRAS and p53 tumours and these hypothesis-generating results should be verified in larger, prospective and randomised phase III trials
Fourrier-Reglat 2011[73-75]	Multicentre France	First-line	Bevacizumab plus FOLFOX/XELIRI	Mean age: 78.3 years	Safety, OS, PFS	Effectiveness and safety of bevacizumab plus

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
(abstract only)	Follow-up 24 months 2006-2007	≥75=12.4%	(n=338) FOLFIRI/XELOX (n=73)	Males: 66.7% PS: ≥2=17.6% (≤75=10.8%)		chemotherapy in elderly patients were similar to those of the rest of the ETNA cohort. Estimations of survival outcomes (1-year OS rate, median OS and PFS) were also comparable to those found in elderly patients (75–80 years) from the BRITE cohort (72.0%, 20.3 months and 10.0 months, respectively)
Kozloff 2011[65] (abstract only) (ARIES study)	Multicentre US 2010	mCRC First-line=76.3% ≥70	Bevacizumab plus chemotherapy (n=2032)	First-line Median age: 75 years (70-92) Males: 57.3% Second-line Median age: 76 years (70-96) Male: 61%	PFS, OS	Within the second-line cohort there were no significant differences between median OS and PFS in patients <70 and ≥70 years. Within the first-line cohort, median OS in patients ≥70 years was significantly lower than in patients <70 years
Rousseau 2011[51]	Phase II France	mCRC ≥70	XELOX (n=60)	Median age: 78 years (70-88) Males: 55% KPS: 100=12%, 90=31%, 80=47%, ≤70=10%, unknown=3%	Primary: stabilisation/ improvement of Katz ADL scale	This study demonstrates the feasibility of XELOX in elderly mCRC patients, with no impairment of independence among patients who remained on therapy
Sastre 2011[49,50]	Phase II Spain 2005-2005 Funded by the Spanish Cooperative Group for Gastrointestinal Tumor Therapy (TTD), Madrid, Spain	mCRC First-line ≥70	Cetuximab (n=41)	Median age: 76 years (70-88) Males: 58.5% KPS: 80=39%, 90=22%, 100=39% Tumour site: colon=80.5%	Primary: RR Secondary: safety, TTP, OS	Cetuximab is a safe monoclonal antibody with moderate activity in first-line mCRC, but the present study does not support the use of cetuximab as single-agent in first-line fit elderly patients with mCRC

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Shin 2011[44]	Phase II Multicentre Korea Median follow-up 11.2 2006-2008 Funded by Korea Health 21 R&D Project	mCRC First-line ≥70=81% [Frail (aged 65-69, PS 2 and)=19%]	S-1 monotherapy (n=48)	Median age: 73 years (65-81) Males: 54% ECOG PS:0=8%, 1=71%, 2=21%	Primary: ORR Secondary: PFS, OS, toxicity	Generally, S-1 monotherapy was well-tolerated and efficacious in the elderly patient group, but not in the frail patient group. Considering PS and co-morbidities in patients >70 years old, S-1 monotherapy may be a first-line therapeutic option for elderly mCRC patients
Takahari 2011[42] (abstract only)	Phase II Single centre Japan 2007-2010	Advanced or recurrent CRC ≥65	Bevacizumab (n=56)	Median age: 75 years	Primary endpoint: PFS Secondary endpoints: TTF, RR, OS, treatment completion status, the incidence and severity of adverse events	Our results suggest that combination therapy with S-1 and bevacizumab can be administered safely and continuously and is therapeutically effective in elderly patients with advanced or recurrent CRC
Vrdoljak 2011[37,38]	Phase II Single centre Croatia Median follow-up 16.3 months 2007-2008	mCRC First-line ≥70	Bevacizumab plus capecitabine (n=41)	Median age: 75 years (70-83) Males: 56% ECOG PS: 0=61%, 1=37%, 2=2% Tumour site: colon=76%, rectum=15%, sigmoid=10%	OS, ORR, PFS	The combination of bevacizumab and capecitabine is effective and has a favourable tolerability profile and should be considered as an option for the initial treatment of mCRC in elderly patients
Feliu 2010[77]	Phase II Multicentre Spain 2006-2008 Funded by Hoffmann-La Roche	mCRC First-line=79% ≥70	Capecitabine and bevacizumab (n=59)	Median age: 75 years (73-79) Males: 58% ECOG PS: 0=44%, 1=53%, 2=3% Tumour site: colon=63%, rectum=25%, both=12%	Primary endpoint: ORR Secondary endpoint: PFS, OS, safety profile	Bevacizumab combined with capecitabine represents a valid therapeutic alternative in elderly patients considered to be unsuitable for receiving polychemotherapy

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Kozloff 2010[62-64] (BRITE study)	Multicentre US Median follow-up 20.1 months 2004-2005 Funded by Genentech Inc.	mCRC First-line <65: n=1057 (54%) 65-74: n=553 (28%) 75-79: n=202 (10%) ≥80: n=61 (8%)	<65 5-FU/LV, FOLFIRI, FOLFOX, I-FL/Saltz, XELOX, Other less aggressive treatments (n=1057) (Overall n=1953)	Median age: 55.3 years (22.5-65.0) Males: 54.2% ECOG PS: 0=50%, 1=37.7%, ≥2=4.9%, unknown=7.4%% Overall tumour site: colon=79.4%	Treatment patterns, safety, PFS, SBP	Elderly patients receiving bevacizumab with first-line chemotherapy showed treatment benefit, although there was reduced median survival with increasing age. There was no increased toxicity among elderly patients, except for risk of arterial thromboembolic events
			65-74 5-FU/LV, FOLFIRI, FOLFOX, I-FL/Saltz, XELOX, Other less aggressive treatments (n=553)	Median age: 69.5 years (65-75) Males: 57.4% ECOG PS: 0=38.5%, 1=47.3%, ≥2=7.1%, unknown=7.1%		
			75-79 5-FU/LV, FOLFIRI, FOLFOX, I-FL/Saltz, XELOX, Other less aggressive treatments (n=202)	Median age: 77.2 years (75.1-79.2) Males: 61.4% ECOG PS: 0=29.7%, 1=47%, ≥2=13.4%, unknown=9.9 %		
			≥80 5-FU/LV, FOLFIRI, FOLFOX, I-FL/Saltz, XELOX, Other less aggressive treatments (n=61)	Median age: 82.5 years (20-95.1) Male: 52.2% ECOG PS: 0=27.3%, 1=49.1%, ≥2=11.8,% unknown=11.8%		
Puthillath 2009[57]	Phase II United States Follow-up 28 months	mCRC First-line ≥70	Capecitabine and bevacizumab (n=16)	Median age=78 years (73-91) ECOG PS: 0=25%, 1=50%, 2=25%	Efficacy, safety	In this underpowered phase II study in elderly patients with mCRC, capecitabine plus bevacizumab was associated with considerable clinical activity but at an increased risk

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	2004-2007 Funded by Genentech Pharmaceutical and a Mentored Scholar Grant from the American Cancer Society					of hand and foot syndrome and arterial thrombotic events
Vamvakas 2009[40] (abstract only)	Phase II Multicentre Median follow-up 11 months	mCRC First-line >70	CAPOX plus bevacizumab (n=36)	Median age: 76 years (70-86)	Efficacy, safety	The combination of CAPOX plus bevacizumab appears to be highly effective, well tolerated when CGA is used for the patients' evaluation. The study is continued until the completion of the planned accrual of 46 patients
Van Cutsem 2009[39] (abstract only)	Multicentre International 2004-2006	mCRC ≥65=33% (≥70=18%, ≥75=7%)	Chemotherapy plus bevacizumab Oxaliplatin-based=50%, Irinotecan-based=35%, Monotherapy=15% (n=1914)	Overall Median age: 59 years (20-85) Males: 58% ECOG PS: 0=65%, 1=34%	Primary: safety Secondary: PFS, OS	These results show that older patients with mCRC can derive similar benefit from bevacizumab + chemotherapy as younger patients without a substantial increase in toxicity and suggest that age alone should not preclude effective treatment
Grande 2009[69,70]	Phase II Spain 2006-2008	mCRC First-line >75 years	XELOX (n=28) (Originally n=19)	Median age: 78.2 years Males=50% PS: 0-2 Tumour site: colon=67.9%	OS, toxicity	Preliminary results suggest that bi-weekly XELOX is an effective first-line treatment for mCRC in elderly patients with an excellent toxicity profile
Berretta 2008[91,92]	Single centre Italy 1998-2005	mCRC ≥70=26%	≥70 FOLFOX2 (n=20)	Median age: 73 years (70-86) Males: 80% WHO PS: 0-1=60%, ≥2=20% Tumour site: colon=65%	Toxicity, response, survival	The FOLFOX2 regimen provides equivalent feasibility, efficacy, and survival gain in middle-aged and in elderly patients with mCRC

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
			<70 (n=58)	Median age: 61 years (37-69) Males: 51.7% WHO PS: 0-1=71.9%, ≥2=28.1% Tumour site: colon=74%		
Francois 2008[72]	Phase II Multicentre France 2002-2005	mCRC First-line ≥70	FOLFIRI1 (n=40)	Median age: 77.3 years (70-84.7) Males: 75% PS: 0=52.5%, 1=40%, Unknown=7.5%	Efficacy	The FOLFIRI-1 regimen is a valid therapeutic option for elderly patients in good clinical condition
Rozzi 2008[98] (abstract only)	Phase II Italy 2006-2008	mCRC Second-line >70	Capecitabine plus cetuximab (n=18)	Median age: 73 years (71-80) Males: 55.6% Median ECOG PS: 1 (0-2) Tumour site: colon: 61%	Efficacy, toxicity	In elderly patients capecitabine plus cetuximab, as second-line chemotherapy, showed an interesting activity with an acceptable profile of toxicity. This regimen could represent an interesting therapeutic option in this setting
Cupini 2007[82,83] (abstract only)	Phase II Italy Median follow-up 31 months	mCRC First-line=20% ≥70	CAPIRI (n=30) XELOX after progression (n=24)	Median age: 76 years (70-82) ECOG PS: 1=83%, 2=17%	Median time to secondary progression	These data indicate that the CGA is a useful instrument to evaluate elderly patients and to select them for treatment. The sequential treatment with ELD-XELIRI followed by ELD-XELOX is feasible in elderly vulnerable mCRC patients and it produces results comparable to those obtained in the younger population
Hochster 2007[68]	Phase II Multicentre USA Follow-up 54 months	aCRC ≥75 years	UFT with LV (n=55)	Median age: 81 years (75-90) Males: 53% ECOG PS: 0=23.6%,	ORR, toxicity	The results of this trial support the efficacy of oral UFT/LV in elderly patients with CRC. The regimen is tolerated moderately well overall, particularly compared with

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	2000-2001 Funded by Bristol-Meyers Squibb Co			1=56.4%, 2=20.0%		other fluoropyrimidine regimens, although there is increased gastrointestinal toxicity in the most elderly. These results suggest that studies using newer oral fluoropyrimidine analogs should be investigated in this patient population
Yoshimatsu 2007[36]	Single centre Japan 1999-2004	mCRC First-line >75	LV plus 5-FU (n=20)	Median age: 77.1 years PS: 0=85%, 1=15%	Efficacy, response to treatment, toxicity	Low-dose LV/5-FU chemotherapy in elderly patients with mCRC could be acceptable in order to avoid adverse effects and to obtain quite a favourable survival time
Feliu 2006[76]	Phase II Multicentre Spain 2003-2003 Funded by Roche, Spain	mCRC First-line ≥70	XELOX (n=50)	Median age: 76 years (70-82) Males: 72% ECOG PS:0=52%, 1=46%, 2=2% Tumour site: colon=68%, rectum=28%, both=4%	Efficacy, safety	XELOX is well tolerated in elderly patients, with respectable efficacy and a meaningful clinical benefit response. Given its ease of administration compared with combinations of oxaliplatin with 5-FU/LV, it represents a good therapeutic option in the elderly
Gebbia 2006[71]	Phase II Multicentre Italy 2001-2002 Median follow-up 12.5 months	aCRC First-line ≥65	Raltitrexed plus LFA and 5-FU (n=70)	Median age: 70 years (65-80) Males: 57% Median ECOG PS: 1 (0-2) Primary tumour site: colon=61%, rectum=39%	Primary: RR according to WHO and side-effects Secondary: duration of response, TTP, OS, QoL	The results of this study suggest that the raltitrexed/5-FU/LFA combination is an effective and well-tolerated regimen for the treatment of elderly patients with aCRC. Its ease of administration and patient's tolerance warrant further investigation over 5-FU/FA regimens
Jensen 2006[66]	Single centre Denmark 2001-2004 Funded by Lisa og	aCRC ≥70 First-line=70% <70 First-line=57% ≥70=22%	Capecitabine or XELOX >70=57 (n=260)	Median age: 73 years (70-82) Males: 61% Site of tumour: colon=70%,	PFS, OS, prognostic factors	Palliative capecitabine-based therapy for aCRC should be considered also for elderly who are in good performance without major comorbidities

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	Gudmund Jørgensens Foundation, P.A.Messerschmidt og hustrus Foundation, fabrikant Einar Willumsens Mindelegat and Dagmar Marshalls Foundation			rectum=30%		
			Capecitabine >75=18 (n=178)	Median age: 75 years (75-82) Males: 56% Site of tumour: colon=65%, rectum=35%		
Ramani 2006[56]	Multicentre UK 1999-2002	Duke's stage: B=34%, C=66% ≥65	5-FU plus FA (n=100)	Median age: 67 years (30-82) Males: 53% WHO PS: 0=46%, 1=36%, 2=15%, 3=1%, NR=2% Tumour site: rectum=23%	Toxicity	This regimen has shown what might be considered high rates of grade 3 and 4 toxicity for an adjuvant treatment, although the delivered dose intensity was acceptable. Caution is urged in the treatment of elderly female patients who have statistically higher rates of grade 3 and 4 toxicity and lower dose intensity
Tsutsumi 2006[41]	Japan 2004-2005 Funded by Ministry of Education, Culture, Sports Science and Technology of Japan	aCRC >70	UFT and LV (n=26)	Median age: 75 years (71-80) Males: 77% WHO PS: 0=73%, 1=19%, 2=8% Tumour site: colon=42%	Safety and efficacy	Oral regimen consisting of UFT/LV is effective and well tolerated in elderly patients with aCRC who are considered ineligible for combination chemotherapy
Berardi 2005[93]	Italy 1999-2003	Mix of disease stages First-line >70	FOLFOX, CPT-11 or FOLFIRI (n=29)	Median age: 76 years (70-82) Males: 8.6% ECOG PS: 0=62%, 1=31, 2=7%	Primary: toxicity Secondary: RR, OS	FOLFOX and FOLFIRI appear to be active and well tolerated regimens for elderly patients with aCRC
Comella 2005[84,85]	Phase II Italy	mCRC ≥70	1st series XELOX (n=35)	Median age: 75 years (70-81)	Efficacy, tolerability	Fit elderly patients with mCRC showed a good response rate to XELOX with only mild

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
	Median follow-up 21 months 2001-2004	(≥80=11%)		Males: 60% ECOG PS:0=43%, 1=51%, 2=6% Tumour site: colon=57%		toxicity observed in most patients. XELOX, should, therefore be considered as an important therapeutic option for elderly patients with mCRC
			2nd series XELOX (n=41)	Median age: 75 years (70-82) Males: 59% ECOG PS: 0=51%, 1=42%, 2=7% Tumour site: colon=71%		
Feliu 2005[79]	Spain 2002-2002	mCRC First-line Aged ≥70 years	Capecitabine (n=51)	Mean age: 76 years (71-89) Males: 61% ECOG PS: 0=27%, 1=59%, 2=14% Tumour site: colon=53%	Tolerability	Our findings suggest that capecitabine is effective and well tolerated in elderly patients with aCRC who are considered ineligible for combination chemotherapy
Mattioli 2005[60]	Phase II Multicentre Italy Follow-up 12.5 months 2001-2004	aCRC First-line ≥70	Bi-fractionated oxaliplatin plus 5-FU/LV (n=78)	Median age: 75 years (70-85) Males: 69% ECOG PS: 0=40%, 1=49%, 2=11% Tumour site: colon=68%	Primary: safety, tumour response Secondary: TTP, OS, duration of response, patient self-maintenance	The bi-fractionated delivery of oxaliplatin plus 5-FU/LV demonstrated high anti-tumour activity in elderly patients with aCRC. Splitting oxaliplatin administration might reduce incidence of severe neuropathy, although this has to be confirmed by further studies
Mendez 2005[59]	Phase II Spain Median follow-up 18.2 1999-2001	mCRC First-line >65=49%(n=53)	>65 CPT-11 plus UFT and LV (n=26)	Median age: 70 years (66-80) Males: 62% WHO PS: 0=39%, 1=46%, 2=15%	Primary: response to treatment Secondary: duration of response, TTP, OS	Weekly CPT-11 plus UFT/LV was found effective and safe as first-line chemotherapy for mCRC. The addition of CPT-11 to UFT/LV doubled the response rate compared with results previously reported with

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
			≤65 CPT-11 plus UFT and LV (n=27)	Overall median age: 65 (44-80) Overall males: 57% WHO PS: 0=59%, 1=37%, 2=4% Overall tumour site: colon=60%		UFT/LV, while myelosuppression remained low
Oh 2005[58] (abstract only)	Multicentre Korea 2001-2004	aCRC First-line >70	Mini-FOLFOX4 (n=27)	Median age: 74 years (70-83) PS: 0=59%, 1=37%, 2=4% Tumour site: colon=63%	Efficacy, toxicity	"Mini-FOLFOX4" is well tolerated with acceptable toxicity without compromising ORR or survival in elderly patients with aCRC
Rosati 2005[52]	Phase II Multicentre Italy Median follow-up 17 months 2002-2004	m/aCRC First-line >70 (>75=47%)	Oxaliplatin plus UFT and FA (n=47)	Median age: 74 years (70-89) Males: 55% ECOG PS: 0=53%, 1=45%, 2=2% Tumour site: colon=64%	Primary: tolerability Secondary: efficacy, QoL	These results confirmed that this tested chemotherapy combination is active with acceptable tolerability and QoL maintenance in elderly patients with advanced or mCRC
Sastre 2005[46,61]	Phase III Multicentre Spain Follow-up 12.3 months 2001-2002	mCRC First-line ≥72	CPT-11 plus 5-FU (n=85)	Median age: 77 years (72-85) Males: 60% ECOG PS: 0=53%, 1=47% Tumour site: colon=67%, rectum=32%, both=1%	Efficacy, toxicity	Twice a month continous-infusion CPT-11 combined with FU is a valid therapeutic alternative for elderly patients in good general condition
Souglakos 2005[43]	Phase II Single centre Greece (Crete) Follow-up 17 months	mCRC First-line ≥70	FOLFIRI (n=30)	Median age: 76 years (70-84) Males: 50% WHO PS: 0=26.6%, 1=53.3%, 2=20.1%	Efficacy, tolerability	The FOLFIRI combination is an active regimen with manageable toxicity as front-line treatment in patients >70 years of age

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	2001-2002			Tumour site: colon=39%, sigmoid=35%, rectum=26%		
Chau 2004[86]	Phase III Multicentre UK 1997-2003 Not stratified for age at randomisation	aCRC Fluoropyrimidine and thymidylate synthase inhibitor-resistant ≥70=21.2%	Irinotecan (n=339)	≥70 median age: 72 years (70-80) <70 median age: 58 years (29-69) Males: 59.3% PS: 0=26.6%, 1=60.5%, 2=11.8%, 3=0.3%, unknown=3 (0.9%) Tumour site: colon=61.7%, rectum=26%, other=10.9%, unknown=1.5%	OS, an irinotecan-specific toxicity composite endpoint	Elderly and PS 2 patients derive the same benefit without experiencing more toxicity with second-line irinotecan treatment for aCRC. Our data do not support the recommendations to give a reduced starting dose to elderly and PS 2 patients
Aparicio 2003[96]	Multicentre France 1999-2002 Funded by Cancer Research UK	mCRC First-line=41% Second-line=51% Third-line=8% 75-79=70% ≥80=30%	Oxaliplatin (n=44) Irinotecan (n=22)	Median age: 75-79=77 years (74-79), ≥80=81 years (80-88) Males: 75-79=52, >80=78 75-79 PS: 0=23%, 1=46%, 2=31% ≥80 PS: 0=11%, 1=50%, 2=22%, 3=17% Overall tumour site: colon=79%	Tolerability, efficacy	We conclude that chemotherapy with oxaliplatin or irinotecan in selected elderly patients is feasible with manageable toxicity. Improvements of PS and prolonged PFS and OS were obtained, but the benefit is weaker after 79 years
Daniele 2003[81]	Multicentre Italy 1998-2000 Funded by AIRC, CTPG and GIOGER	aCRC Stage IV First-line ≥70	"de Gramont" schedule FU/FA (n=34)	Median age: 76 years (70-85) Males: 67.6% PS: ECOG: 1=70%, 2=30%	Activity, toxicity	The de Gramont scheme is active and tolerated in elderly patients with aCRC. This regimen is active and can be considered reasonably safe in this population. This population should be the subject of specific chemotherapy studies, both in the metastatic and adjuvant setting

Study	Study details	Population	Intervention	Baseline data	Outcomes	Author conclusions
Feliu 2002[78]	Multicentre Spain 1997-1999	aCRC First-line=32% ≥70 (70-75=57%, 76-80=29%, ≥80=13%)	Raltitrexed (n=92)	Median age: 77 years (71-88) Males: 52% ECOG PS: 0=20%, 1=70%, 2=11% Primary tumour site: colon=52%, rectum=48%	To analyse the efficacy and tolerance of raltitrexed in elderly patients with aCRC	Raltitrexed is an active, convenient and low toxicity treatment for the elderly with aCRC. However, it must be used cautiously in elderly patients with a creatinine clearance 41.08 ml/s since they are at a higher risk of grade 3-4 toxicity

mCRC=metastatic colorectal cancer; aCRC=advanced colorectal cancer; 5-FU=5-fluorouracil; FOLFOX=folinic acid (leucovorin), 5-FU and oxaliplatin; FOLFIRI=Irinotecan plus 5-FU; XELOX=oxaliplatin and capecitabine; I-FL=irinotecan and leucovorin; FU/FA=5-FU and leucovorin; CAPIRI=capecitabine and irinotecan; FA=folic acid; UFT=tegafur/uracil; CAPIRI=capecitabine and irinotecan; XELIRI=capecitabine plus irinotecan; LFA=levofolinic acid; LV=leucovorin; TEGAFOX-E=cetuximab, oxaliplatin and UFT; PFS=progression-free survival; OS=overall survival; TTP=time to progression; TTF=time to treatment failure; ORR=overall response rate; ADL=activities of daily living; CRR=complete response rate; CGA=comprehensive geriatric assessment; WHO=World Health Organisation; ECOG=Eastern Cooperative Oncology Group; PS=performance status; KPS=Karnofsky PS; QoL=quality of life; NA=not applicable; NR=not reported; SBP=spontaneous bacterial peritonitis; RR=response rate

9.2 Efficacy evidence

Forty-seven single cohort studies[36-55,57-97] reported outcomes of interest. Efficacy outcomes are presented in Table 16.

Efficacy outcomes were well reported. Most older patients achieved less than 10 months PFS/TTP, with only nine studies[37-39,43,53-55,62-64,73-75,77,88,94] achieving ≥10 months. Where comparisons with younger patients were made, in general the results were similar. For median OS, where comparisons between age groups were available, the older and younger patients achieved similar results. Ten studies[37-39,57,60,62-64,88,90,91,98] reported that older patients achieved a median OS of ≥20 months. In terms of ORR, the lowest reported figure was 11%[41] and the highest was 72%,[66] with similar results reported for older versus younger patients.

Table 16 Efficacy evidence, single cohorts

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Rosati 2013[53-55]	XELOX plus bevacizumab followed by bevacizumab alone	11.5 (10.0 to 12.9)	NR	19.3 (16.5 to 22.1)	NR	52 (37 to 68)	NR
Abdelwahab 2012[97]	Cetuximab plus irinotecan	4.0 (3.0 to 5.6)	NR	7.0 (5.9 to 8.0)	NR	41 (39 to 44)	NR
Benavides 2012[95]	Oxaliplatin plus 5-FU	9.1 (8.0 to 10.0)	NR	16.3 (14.0 to 21.0)	NR	52	NR
Berretta 2012[90]	Oxaliplatin	7 (1 to 37)	NR	27 (1 to 124)	NR	57.3	NR
Chang 2012[87]	Capecitabine Stage II	3-year DFS: 75.2% 3-year RFS: 79.0%	NR	5-year OS=75.1%	NR	NR	NR
	Capecitabine Stage III	3-year DFS: 56.2% 3-year RFS: 60.4%		5-year OS=70.1%			
Jehn 2012[67]	Cetuximab >65	7.0	p=0.12	NR	NR	35.4	NR
	Cetuximab ≤65	6.5				37.9	
Sastre 2012[47,48]	Cetuximab plus capecitabine	7.1 (5.3 to 8.4)	NR	16.1 (12.0 to 18.8)	NR	31.8 (20.9 to 44.4)	NR
Scartozzi 2012[45]	5-FU/5-FU plus irinotecan/irinotecan plus oxaliplatin	TTP: 5.5	NR	17	NR	Partial=17 (2 to 32)	NR
Bennouna 2011[94] (abstract only)	Chemotherapy plus bevacizumab ≥70	10.0 (8.9 to 11.8)	NR	NR	NR	NR	NR
	<70	11.4 (10 to 12.3)					
	≥75	9.5 (7.9 to 11.3)					
Berretta 2011[89]	FOLFOX 4	7.5	NR	16	NR	44.4	
Carreca 2011[88] (abstract only)	Capcitabine and oxaliplatin plus bevacizumab	12.3	NR	23.5	NR	TRR=50.1	NR
Di Bartolomeo 2011[80] (abstract only)	TEGAFOX-E	NR	NR	NR	NR	44	NR

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Fourrier-Reglat 2011[73-75] (abstract only)	Bevacizumab plus FOLFOX/XELIRI or FOLFIRI/XELOX >75	10.6 (9 to 12.8)	NR	1-year OS=78% (63.9 to 87.2)	NR (median OS not reached by either group)	NR	NR
	≤75	9.9 (9.3 to 11.1)		1-year OS=80.5% (76.0 to 84.2)			
Kozloff 2011[65] (abstract only)	First-line chemotherapy plus bevacizumab ≥70	9.9 (8.9 to 10.4)	1.11 (0.99 to 1.25)	19.6 (18.1 to 21.6)	1.29 (1.13 to 1.48)	NR	NR
	<70	10.3 (9.8 to 10.9)		25.1 (23.1 to 26.9)			
	Second-line chemotherapy plus bevacizumab ≥70	7.9 (6.7 to 9.2)	0.94 (0.77 to 1.15)	17 (13.4 to 21.8)	1.1 (0.88 to 1.37)		
	<70	7.9 (7.2 to 8.3)		18.7 (17 to 21.4)			
Rousseau 2011[51]	XELOX	7.3 (6.5 to 9.2)	NR	12 (11.8 to 12.2) 1-year OS=75% (64 to 87)	NR	37	NR
Sastre 2011[49,50]	Cetuximab	TTP: 2.9	NR	11.1	NR	14.6 (5.6 to 29.2)	NR
Shin 2011[44]	S1-monotherapy All patients	3.9 (3.0 to 4.8)	p=0.016	11.3 (7.4 to 15.2)	p=0.01	18.7 (9.0 to 32.6)	NR
	70-85	4.3 (3.0 to 5.4)		13.1 (9.5 to 16.7)		17.9	
	65-69 & PS 2	1.4 (0.8 to 2.0)		4.1 (3.2 to 5.0)		22.2	
Takahari 2011[42] (abstract only)	Bevacizumab	TTF: 7.6 (6.1 to 9.1)	NR	NR	NR	54 (40 to 67)	NR
Vrdoljak 2011[37,38]	Capecitabine plus Bevacizumab	11.5 (4.9 to 18.0)	NR	21.2 (9.5 to 32.9)	NR	65	NR
Feliu 2010[77]	Capecitabine plus Bevacizumab	10 (7.6 to 14.1)	NR	18 (9.6 to 26.3)	NR	34 (22.4 to 47.5)	NR
Kozloff 2010[62-64]	5-FU/LV, FOLFIRI, FOLFOX, I-FL/Saltz, XELOX, <65	PFS: 10.2 (9.5 to 10.7) TTP: 10.4 (9.9 to 11.1)	NR	26 (24.5 to 27.6)	NR	48.3	NR
	65-74	PFS: 9.6 (9.0 to 10.3) TTP: 10.6 (9.9 to 11.4)		21.1 (18.6 to 23.9)		43.8	
	≥75	PFS: 9.7 (8.5 to 10.4)		19.2 (16.2 to 21.1)		NR	
	75-79	TTP: 11.2 (10.1 to 12.2)		20.3		41.6	
	≥80	TTP: 9.9 (8.5 to 12.4)		16.2		34.1	

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Puthillath 2009[57]	Capecitabine plus bevacizumab	TTP: 9.5 (6.1 to 18.0)	NR	21.2 (14.4 to 30.9)	NR	25	NR
Vamvakas 2009[40] (abstract only)	CAPOX plus bevacizumab	TTP: 9.9 (7.4 to 12.8)	NR	1-year OS=82% 2-year OS=59% (Median OS not achieved)	NR	43 (34 to 66)	NR
Van Cutsem 2009[39] (abstract only)	Chemotherapy plus bevacizumab <65	10.8	NR	23.5	NR	NR	NR
	65-74	10.8		22.8			
	≥75	10.0		16.6			
Grande 2009[69,70]	XELOX	TTP: 8.6	NR	NR	NR	41.6	NR
Berretta 2008[91,92]	FOLFOX2 ≥70	TTP: 6	p=0.83	21.8	p=0.67	55.0	NR
	<70	TTP: 5.9		20.9		43.9	
Francois 2008[72]	FOLFIRI1	8 (6 to unreached)	NR	17.2 (11.6 to 22.2)	NR	40 (25 to 55)	NR
Rozzi 2008[98] (abstract only)	Capecitabine plus cetuximab	6.9 (3.0 to 10.0)	NR	21.1 (6.0 to 18.0)	NR	22	NR
Cupini 2007[82,83] (abstract only)	First-line: CAPIRI	7.3	NR	NR	NR	27	NR
	Second-line: Oxaliplatin plus capecitabine	4.9		19.3		10	
Hochster 2007[68]	UFT plus LV	4.6 (2.6 to 6.7)	NR	13 (9.6 to 17.4)	NR	22 (11.8 to 35)	NR
Yoshimatsu 2007[36]	LV plus 5-FU	NR	NR	18.4	NR	15	NR
Feliu 2006[76]	XELOX	TTP: 5.8 (3.9 to 7.8)	NR	13.2 (7.6 to 16.9)	NR	36 (28 to 49)	NR
Gebbia 2006[71]	Raltitrexed plus levofloinic acid and 5-FU	TTP: 6.5 (1 to 12)	NR	12.5 (1.0 to 20.0)	NR	35.0 (29.5 to 40.5)	NR
Jensen 2006[66]	Capecitabine or XELOX ≥70	5.5	1.09 (0.71 to 1.68), p=0.84	8.4	1.48 (1.04 to 2.38)	37	p=0.61
	<70 years	6.0		12.5		33	
	Capecitabine ≥75	8.4	0.35 (0.29 to 0.80), p=0.001	15.5	0.68 (0.42 to 1.21), p=0.18	72	p=0.0006
	<75 years	4.1		10.4		31	

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Tsutsumi 2006[41]	UFT plus LV	PFS/TTP=3.9 (1.9 to 5.9)	NR	9.8 (7.8 to 11.8)	NR	11 (19.7 to 24.5)	NR
Berardi 2005[93]	FOLFOX or FOLFIRI or CPT-11	NR	NR	21	NR	NR	NR
Comella 2005[84,85]	XELOX 1st series	6.9	NR	14.1	NR	40 (24 to 58)	NR
	2nd series	8.5 (6.7 to 10.3)		14.4 (11.9 to 16.9)		41 (30 to 53)	
Feliu 2005[79]	Capecitabine	TTP: 7.0 (6.4 to 9.5)	NR	11.0 (8.6 to 13.3)	NR	24 (15 to 41)	NR
Mattioli 2005[60]	Bi-fractionated oxaliplatin plus 5-FU/LV	TTP: 8.0 (0.5 to 22.0)	NR	20 (1 to 29)	NR	51 (41 to 63)	NR
Mendez 2005[59]	CPT-11 plus UFT LV All	TTP: 7.9 (6.6 to 9.1)	NR	18.2 (13.8 to 22.6)	NR	21 (10 to 32)	NR
	>65	7.6 (5.0 to 10.0)		16.7 (12.0 to 22.0)		23 (7 to 39)	
	≤65	7.9 (6.5 to 9.2)		18.2 (9.1 to 27.4)		19 (4 to 33)	
Oh 2005[58] (abstract only)	Mini-FOLFOX4	PFS: 7.1 (4.3 to 9.9)	NR	13.5 (10.8 to 16.2)	NR	31.8	NR
Rosati 2005[52]	Oxaliplatin plus UFT and FA	TTP: 8 (6.7 to 9.3)	NR	14.1 (11 to 17.1)	NR	51 (40.7 to 61.2)	NR
Sastre 2005[46,61]	Irinotecan plus 5-FU	TTP: 8 (6 to 10)	NR	15.3 (13.8 to 16.9)	NR	35 (25 to 46)	NR
Souglakos 2005[43]	FOLFIRI	TTP: 17.0 (2.0 to 22.5)	NR	14.5 (1.5 to 29.5)	NR	36.6 (26.6 to 48.4)	NR
Aparicio 2003[96]	Oxaliplatin or irinotecan 75-79	PFS: 7.3	NR	12.1	NR	22	NR
	80-88	PFS: 4.5		9.9			
Daniele 2003[81]	"de Gramont" schedule	TTP: 4	NR	12.6	NR	20.6 (8.7 to 37.9)	NR
Feliu 2002[78]	Raltitrexed	3.5 (0.7 to 8.3)	NR	9.4 (range 0.5 to 37.7) 1 year OS=30% (21 to 91)	NR	PR=22 (17 to 36)	NR

XELOX/CAPOX=capecitabine plus oxilaplatin; 5-FU=fluorouracil; FOLFIRI=fluorouracil plus irinotecan; TEGAFOX-E=cetuximab plus oxaliplatin and flurorpirimidine; FOLFOX=fluorouracil plus oxaliplatin; XELIRI=capecitabine plus irinotecan; CTP-11=irinotecan; UFT=tegafur-uracil; LV=leucovorin; PFS=progression-free survival; RFS=relapse-free survival; DFS=disease-free survival; TRR=tumour response rate; TTP=time to progression; TTF=time to treatment failure; OS=overall survival; ORR=overall/objective response rate; NR=not reported; CI=confidence interval

[a]Values are PFS, unless otherwise stated

9.3 Tolerability evidence

A total of 37 studies[37,38,40-42,44-51,53-57,59-61,66-79,81-85,87,90-97] reported tolerability outcomes. Results are presented in Table 17.

Although many of the studies reported the median number of cycles per patient, or the proportion of patients who received certain numbers of cycles, only four studies[49-51,91,95] reported outcomes relating to dose intensity or proportion of planned doses received. In the study by Benavides et al,[95] 74% of patients received the full dose, and in the study by Sastre et al,[48,49] all patients received an RDI of 100%. In the study by Feliu et al,[78] 84% of patients received ≥90% of the planned dose. Berretta et al[91] reported that older patients achieved a slightly higher RDI than younger patients (84% vs 81%). Twenty-two studies[41,44,46,51,53-57,59-61,66-68,71-75,77-79,81,84,85,87,95] reported outcomes relating to discontinuations or withdrawal from treatment. Adverse events or disease progression were the most common reasons for discontinuations and/or withdrawals.

Treatment modification and interruption rates were fairly well reported in the studies. However, reasons for modification and interruption were not always reported; where stated, AEs and patient requests were the most common reasons. In terms of AEs, only five studies[41,69,70,78,79,81] did not report AE rates >10%. The most commonly reported AE was grade 3-4 diarrhoea, which was generally reported to be <20%; Cupini et al[82,83] reported a much higher figure of 37% for first-line XELIRI (irinotecan plus capecitabine). Some studies reported the figures for any grade 3-4 AE, and results were available for both older and younger patients, and despite the variance between studies, the figures were similar for older and younger patients.[67,73,74,94]

Table 17 Tolerability evidence, single cohorts

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Rosati 2013[53-55]	XELOX plus bevacizumab followed by bevacizumab alone Median cycles per patient=8 (1-8)	Discontinuation: Withdrawal of consent=1 patient (after 3 cycles) Death=1 patient (after 21 days) Suicide=1 patient (after 2 cycles)	20% dose capecitabine and oxilaplatin decrease for all grade 3-4 toxicities	Any grade 3-4 AE=23%
Abdelwahab 2012[97]	Cetuximab plus irinotecan Median cycles per patient=8 (2-24)	NR	25% irinotecan dose reduction in 64 cycles (14%) Delayed irinotecan in 51 cycles (11%) Delayed cetuximab in 12 cycles (3%)	Grade 3 skin rash=20% Grade 3 diarrhoea=18%
Benavides 2012[95]	Oxaliplatin plus 5-FU Median cycles per patient=10 (1-32) 74% received full doses	Treatment discontinuation, due to: AE=43% Disease progression=27% Maximal benefit achieved=12% Patient decision (10%), Surgery=5% Others=3%	Dose delays and/or reductions were mainly due to haematological and non-haematological (mostly neurological) toxicities	Neutropenia=17% Neurotoxicity=18% Diarrhoea=11% Asthenia=10%
Berretta 2012[90]	FOLFOX4 or FOLFOX2 (leucovorin, 5-FU and oxaliplatin) Total of 712 cycles	NR	25% reduction in 17 (22.7%) due to grade 3+ haematological toxicity	Neutropenia=20%
Chang 2012[87]	Capecitabine Median cycles per patient=8 (1-8) 82% completed 8 cycles.	Discontinuation due to; Relapse, declined treatment and aggravation of comorbidities	Dose escalation in 68% of patients	Grade 3 hand-foot syndrome=25.6%
Jehn 2012[67]	NR	Cetuximab 92% of cases before the end of 12-month observational period, mainly due to disease progression	Cetuximab dose modification in 106 cases: Skin toxicity=30% Treatment interruption: Patient request=23.6%	Grade 3-4 Gastrointestinal: >65=9% ≤65=10% Skin toxicity: >65=10.9% ≤65=8.8% Any toxicity: >65=19.7% ≤65=21% (p=0.68)

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Sastre 2012[47,48]	NR	NR	Cetuximab Dose reduction capecitabine 18 patients (66.6%) Cetuximab reduction 18 patients (27.3%)	Paronychia=29.6% Dermatitis acneform=29.6% Hand-foot syndrome=22.2% Diarrhoea=18.5%
Scartozzi 2012[45]	NR	NR	NR	Modified FOLFOX6 Leukopenia=45.5% Neutropenia=45.5% Nausea=27.5% Vomiting=18.2% Fatigue=36.4% 1 death, neutropenia (FOLFOX6)
	NR	NR	NR	Modified FOLFIRI Leukopenia=16.7% Neutropenia=16.7% Diarrhoea=16.7% Fatigue=50%
	NR	NR	NR	Modified 'de Gramont' regimen Leukopenia=100 Diarrhoea=100
Bennouna 2011[94] (abstract only)	NR	NR	NR	Chemotherapy plus bevacizumab ≥70 Any grade 3-4 AE=11.2% <70 Any grade 3-4 AE=8.7% ≥75 Any grade 3-4 AE=11.5%
Fourrier-Reglat 2011[73-75] (abstract only)	NR	Bevacizumab plus FOLFOX/XELIRI or FOLFIRI/XELOX 43 patients discontinued first-line treatment (9.3% of which discontinued bevacizumab)	Treatment-free intervals >75=39.2%	Any grade 3-4 AE >75=43.1%
			≤75=28.6%	≤75=41.7%
Rousseau 2011[51]	XELOX Total cycles=290 >3 cycles=90% 6 cycles=63% Initial dose=75% Planned dose increase at cycle 4=14 (31%)	Discontinuation=22, due to: Disease progression=5 (8%) Toxicity=11 (18%) Patient request=2 (3%) Other reasons=4 (7%)	NR	Grade 3-4 diarrhoea=14%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Sastre 2011[49,50]	Cetuximab RDI=100%	NR	Dose reduction in 2 (4.8%) patients due to toxicity 1 week dose delay=29%, due to cutaneous toxicity	Grade 3 skin toxicity=12.2%
Shin 2011[44]	S1-monotherapy All patients Median cycles=4 (1-20)	Discontinuation due to: Disease progression=77% Patient refusal=8% Other=4%	Treatment delays=22 (12.0%) Median delayed weeks=1 (0.6 to 3.0)	Any grade 3 AE=29%
	70-85 Median cycles=5 (2 to 20)		Treatment delays=20 (12.2%) Median delayed weeks=1 (0.6 to 3.0) Dose modification=12% of cycles, due to: AE=19%	NR
	65-69 + PS 2 Median cycles=2 (1-14)		Treatment delays=2 (14.3%) Median delayed weeks=1 (0.9-1.4)	Death due to toxicity=2 patients (pneumonia and sepsis)
Takahari 2011[42] (abstract only)	NR	NR	NR	Bevacizumab Hypertension=18%
Vrdoljak 2011[37,38]	Capecitabine plus bevacizumab Median cycles=12 (2 to 30)	NR	Treatment related delays=43.9% Dose reduction=59%	Hand-foot syndrome=17% DVT=12% Treatment-related deaths=2
Feliu 2010[77]	Capecitabine plus bevacizumab Median cycles=7.1 (±6.5)	Discontinuation due to: Disease progression=43% AEs=19% Patient refusal=9% Protocol violation=9% Other=17%	Capecitabine dose reduction/discontinuation=59% Bevacizumab dose discontinuation=24%	Grade 3-4 hand-foot syndrome=19%
Puthillath 2009[57]	Capecitabine and bevacizumab Median cycles=12 (3 to 69)	Discontinuation: Early progression of disease=1 Bevacizumab toxicity=1	NR	Grade 3 diarrhoea=13% Grade 3 hand-foot syndrome=25% Grade 3 hypertension=13%
Vamvakas 2009[40] (abstract only)	NR	NR	NR	CAPOX and bevacizumab Grade 3-4 diarrhoea=11%
Grande 2009[69,70]	XELOX Median cycles=8 (5.25 to 12.00)	NR	NR	NR
Berretta 2008[91,89]	FOLFOX2 ≥70 Median cycles=4 (2 to 9) Median DI=84% (55 to 106)	NR	Dose reduction=1 (50% reduction) Delays=15 (48%), due to: Willingness=38%	Grade 3-4 diarrhoea=2 (10%)

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
			Late haematological recovery=16%	
	<70 Median cycles=3 (1 to 7) Median DI=81% (54 to 94)		Dose reduction=4 (25% reduction), due to grade 3 diarrhoea and previous myocardial infarction Delays=18 (38%), due to: Willingness=25% Late haematological recovery=17%	Grade 3-4 diarrhoea=3 (3.4%) (Toxicity was not significantly different with regard to age)
Francois 2008[72]	FOLFIRI1 Median cycles=8 (1 to 18)	Discontinuations due to: Disease progression, unacceptable toxicity (grade 4 or >2 weeks), significant change to the QoL or withdrawal of patient consent	Postponed cycles=6.3% (84% due to toxicity) Dose reduction=7% (95% due to toxicity) Postponed and reduction=3%	Diarrhoea=15% Asthenia=15%
Cupini 2007[82,83] (abstract only)	First-line=CAPIRI Median cycles=9	NR	Continuation to second line due to progression or toxicity Irinotecan dose reduced due to excessive incidence of diarrhoea	Diarrhoea=37%
	Second line=XELOX Median cycles=5			<10%
Hochster 2007[68]	UFT plus LV Median cycles=3 (1 to 29)	Discontinuations due to: Progressive disease=73% Withdrawal of consent=13% Complications/toxicity=5% Death without progression=5% Discontinuation of drug supply=2%	Dose modifications=45%: Reductions=16 Delays=9	Any grade 3-4 AE=36% Grade 3 diarrhoea=13%
Feliu 2006[76]	XELOX Median cycles=5 (1 to 8)	NR	NR	Diarrhoea=22% Asthenia=16% Nausea/vomiting=14%
Gebbia 2006[71]	Raltitrexed plus LFA and 5-FU Median cycles=8 (1 to 12)	Discontinuation due to: Early progression=3 Patient refusal=2	Delays of 14 days=22% 25% dose reduction of raltitrexed and 5-FU=5 Second-line chemotherapy=43	Grade 3 neuropathy=10% Grade 3 asthenia=11% Grade 3 transaminases=10%
Jensen 2006[66]	Capecitabine or XELOX No significant difference for number of courses <70 and ≥70 years p=0.44 ≥70 No. of cycles: ≤3=39%, 4-6=37%, 7-9=16%. 10-12=9%	Toxicity n=6 (14%)	Capecitabine RDI: 100%=31 (54%), 75%=21 (37%), 50%=5 (9%) Oxaliplatin RDI: 100%=10 (71%), 75%=3 (21%), 50%=1 (7%)	Cutaneous PPE=11%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
	<70 No. of cycles: ≤3=64%, 4-6=39%, 7-9=20%, 10-12=7%	Toxicity=11 (8%)	Capecitabine RDI: 100%=127 (63%), 75%=60 (30%), 50%=16 (8%)	Cutaneous PPE=15%
	Capecitabine: ≥75 years had significantly more courses than younger patients p=0.0003 ≥75 No. of cycles: ≤3=11%4-6=22% 7-9=39%, 10-12=28%	Toxicity n=1 (6%)	RDI: 100%=7 (39%), 75%=9 (50%), 50%=2 (11%)	NR
	<75 No. of cycles: ≤3=35%4-6=36% 7-9=21%, 10-12=8%	Toxicity=16 (10%)	RDI: 100%=102 (64%), 75%=40 (25%), 50%=18 (11%)	NR
Ramani 2006[56]	NR	5-FU plus FA Discontinuation=18% due to: Progressive disease=5% Personal=4% Unacceptable toxicity=7% Venous access problems=1%	Dose reduction=41% (20% reduction in 38%, 25% reduction in 3%) Second dose reduction=11% (20% reduction in 10%, 30% reduction in 1%)	Grade 3-4 diarrhoea=20% Grade 3 fatigue=14%
Tsutsumi 2006[41]	UFT and LV Median cycles=4 (1 to 12)	Discontinuation after <3 cycles=34%, due to: Disease progression=56% Refusal=44%	Treatment delays=11% (non-treatment related)	NR
Berardi 2005[93]	FOLFOX or FOLFIRI or CPT-11 Median cycles=5.5 (1 to 12)	NR	NR	Grade 3 neutropenia=10.1% Grade 3 diarrhoea=10.3%
Comella 2005[84,85]	XELOX 1st series Median cycles=6 (1 to 12)	Discontinuations due to: Protocol=77% Withdrawal of consent=6% Disease complications=12% Stroke=6%	NR	Any grade 3 AE=29% Grade 3 neuropathy=11%
	2nd series Median cycles=6 (1 to 10)		NR	NR
Feliu 2005[79]	Capecitabine Median cycles=5 (1 to 8)	Discontinuation=18%, due to: Disease progression=10% AE=4% Patient refusal=2%	Treatment delay=45.0%, due to: Unrelated=60.9% Neutropenia=8.7% Non-haematological AE=30.4%	NR

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Mattioli 2005[60]	Bi-fractionated oxaliplatin plus 5-FU and LV Median cycles=8 (1 to 19)	Discontination due to: Disease progression=34 Patient refusal=12 Unacceptable toxicity=8 Local treatment of metastases=4 Worsening of comorbidities=1	NR	Grade 3 neutropenia=7.9% Grade 4 neutropenia=14.1% Grade 3 diarrhoea=6.4% Grade 4 diarrhoea=3.8% Grade 3 leukopenia=5.1% Grade 4 leukopenia=6.4%
Mendez 2005[59]	CPT-11 >65 Median cycles=3	Discontinuations=9, due to: Voluntary withdrawal=4 AEs=5	Suspended infusions=31 cycles in 21 patients (40%) CPT-11 dose reduction=23% (6% of cycles), due to: Non-haematological and/or haematological AE UFT dose reduction=15% (4% of cycles), due to: Non-haematological AEs CPT-11 & UFT dose reductions=9% (2% of cycles) Delay=60% (21% of cycles), due to: Non-haematological toxicity/unrelated	Grade 3-4 neutropenia=19% Grade 3-4 diarrhoea=35% Grade 3-4 nausea/vomiting=15%
	≤65 Median cycles=6 (p=0.052)			Grade 3-4 neutropenia=4% Grade 3-4 diarrhoea=22% Grade 3-4 nausea/vomiting=19%
Sastre 2005[46,61]	CPT-11 plus 5-FU Median cycles=12 (1 to 33)	Discontinuations=12, due to: Death=4 Surgery=1 AEs=7	Delayed cycles=12%, due to haematological toxicity in 52% of delays Dose reduction=22%	Neutropenia=21% Diarrhoea=18% Asthenia=13%
Aparicio 2003[96]	Oxaliplatin or irinotecan 75-79 Mean cycles=10.2±0.8	NR	Dose reduction=35% of cycles	Neutropenia=17% Diarrhoea=15% Neuropathy=10%
	≥80 Mean cycles=12.5±2.2			Neutropenia=17% Diarrhoea=11% Neuropathy=11% Thrombocytopenia=11%
Daniele 2003[81]	'de Gramont' schedule Median cycles=6	Discontinuations=18, due to: Toxicity=5 Tumour progression=11 Patient refusal=2	NR	NR

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Feliu 2002[78]	Raltitrexed Median cycles=5 (1 to 13) Median dose intensity=0.92 mg/week (0.75 to 1.00) ≥90% or more of planned dose=84%	Discontinuation after <3 cycles=11, due to: Toxic death=3 Progression=4 Patient refusal=2 Death not related to neoplasia=2	Delays=16%	Toxic death=3

AE=adverse event; RDI=relative dose intensity; QoL=quality of life; DVT=deep vein thrombosis; FOLFOX=folinic acid, 5-FU and oxaliplatin; FOLFIRI=folinic acid, 5-FU and irinotecan; XELIRI=irinotecan plus capecitabine; XELOX/CAPOX=oxaliplatin plus capecitabine; UFT=Tegafur-uracil; LV=leucovorin/folinic acid; FA=folinic acid/leucovorin; CPT-11=irinotecan; 5-FU=5-fluorouracil; 'de Gramont' schedule=continuous and bolus 5-FU and folinic acid; PS=performance status; PPE=palmar-plantar erythrodysesthesia; NR=not reported

9.4 Comprehensive geriatric assessment and quality of life

Summary details of outcomes relating to CGA and QoL are presented in Table 18.

9.4.1 Comprehensive geriatric assessment

Eight studies[47,52,60,76,79,81,84,85,88] reported information relating to CGA. There were a number of CGA tools utilised across the studies, including: the Katz Scale, CCI, Activities of Daily Living (ADL), IADL, and the Mini-Mental State (MMS). Two studies[47,88] used CGA to determine patient eligibility for entry into the study, three studies[52,76,81] used the tools as an assessment measure at study entry, and three studies[60,79,84,85] used CGA tools as a pre-treatment and follow-up assessment measure.

9.4.2 Quality of life

Quality of life was reported by six studies.[43,52-55,72,87,88] The most common tool used to measure QoL was the EORTC QLQ-C30, which was used in five studies,[43,52-55,87,88] and one study used the Spitzer Uni-scale.[72] Where reported, authors conclusions suggest that the occurrence of side-effects did not influence QoL, and there were no significant changes in QoL during chemotherapy.

Table 18 Comprehensive geriatric assessment and quality of life, single cohorts

Study	Geriatric assessment		Quality of life	
	Tool(s) used	**How tool was used**	**Tool(s) used**	**Author conclusions**
Rosati 2013[53-55]	NR	NR	EORTC QLQ-C30	Neither response to treatment nor occurrence of side-effects significantly influenced changes in patients' QoL
Chang 2012[87]	NR	NR	'Korean version' of EORTC QLQ-C30	During chemotherapy, no significant worsening of functional and global QoL occurred; a slight deterioration in functional scales observed at 3 months recovered with the passage of time
Sastre 2012[47,48]	Independent Daily Activities Katz Scale	Used to determine eligibility for study	NR	NR
Carreca 2011[88] (abstract only)	Unspecified CGA	Used to determine eligibility for study	EORTC QLQ-C30	NR
Francois 2008[72]	NR	NR	Spitzer Uni-scale	NR
Feliu 2006[76]	Charlson comorbidity Index, ADL and IADL	Used as a patient assessment measure at study entry	NR	NR
Feliu 2005[79]	ADL	Used as pre-treatment and follow-up assessment measure	NR	NR
Mattioli 2005[60]	ADL, IADL	Used as pre-treatment and follow-up assessment measure	NR	NR
Rosati 2005[52]	ADL IADL	Used as a patient assessment measure at study entry	EORTC QLQ-C30	Occurrence of side-effects did not influence QoL. Number and type of comorbidities, dependence in ADL, and % inability in IADL were not significantly related to occurrence of adverse events
Souglakos 2005[43]	NR	NR	EORTC QLQ-C30	QoL remained constant or presented slight improvement during treatment. The majority of patients had improvement of tumour-related symptoms, which was associated with tumour growth control
Comella 2005[84,85]	ADL, MMS, CCI	Used as pre-treatment and follow-up assessment measure	NR	NR
Daniele 2003[81]	ADL, IADL	Used as a patient assessment measure at study entry	NR	NR

CGA=comprehensive geriatric assessment; ADL=Activities of Daily Living; IADL=Instrumental Activities of Daily Living; MMS=Mini-Mental Status; CCI=Charlson Comorbidity Index; EORTC QLQ-C30= EORTC quality of life cancer questionnaire; QoL=quality of life; NR=not reported

9.5 Discussion

The 49 cohort studies[36-98] included in the review have provided an abundance of clinical evidence; however, the studies were predominantly small and heterogeneous, which did not allow for useful synthesis of the clinical evidence available. Clinical consensus suggests that the data from single cohort studies are difficult to interpret in any meaningful way; however, the data have been included in this report for completeness and to show the extent of the evidence base.

10 RETROSPECTIVE DATA

Seventeen studies[99-118] that reported retrospective data relating to older people with CRC were included in the review. Study characteristics are presented in Table 19. Three studies[102,104,114] were published in abstract format only. Data were poorly reported in most of the studies.

10.1 Study characteristics

Information about the study populations and baseline data relating to patients were not well reported, with significant gaps in the information provided. Four studies[101,103,115,116,118] explicitly reported that they were multicentre, five studies[106,110-113,117] were single centre, and nine studies[99,100,102,104,105,107-109,113,114] did not report this information. The majority of studies were conducted in Europe, however one study was conducted in Australia,[109] one in the USA,[99] and three studies were conducted in East Asia.[108,110-112] The three studies that reported information on funding were all supported by pharmaceutical companies.[99,101,103,109]

Where explicitly stated, the majority of studies focussed on older patients with mCRC; however, four studies focussed on patients with aCRC.[108,109,115,116] Eleven studies[99-105,107-109,112,113,115,116] used the cut-off age of ≥70 to define 'older', and six studies[106,110,111,113,114,117,118] used the cut-off age of ≥65 years. The studies were predominantly small, with only six studies enrolling more than 100 patients in total.[99,105,106,109-111,117] Where data were reported, the majority of patients across the studies had a good PS (0-1).

Table 19 Study characteristics, retrospective studies

Study	Study details	Population summary	Intervention (n)	Baseline data	Purpose	Author conclusions
Romiti 2002[115]	Multicentre Italy 1998-2000	Predominantly aCRC ≥70=55.6%	Raltitrexed (n=90)	Median age: 70 years (36-85) Males: 56% ECOG PS: 0-1=76%, 2=24% Tumour site: colon=74%	Toxicity of raltitrexed in relation to age, sex and chemotherapy setting	The raltitrexed toxicity profile does not appear to be significantly influenced by age; however, caution is recommended in the management of elderly patients, particularly in the presence of impaired renal function
Comella 2003[105]	Italy	mCRC >70=14.4%	IRIFAFU (n=118) <54=37 55-69=64 >70=17	Median age: Overall=62 years (28-79) <54=48 years (28-54) 55-69=64 years (55-69) >70=68 years (65-79) Males=69% Overall PS: 0=59%, 1=37% 2=3% <54 PS: 0=54%, 1=41%, 2=54% 55-69 PS:0=59%, 1=38%, 2=3% >70 PS: 0=71%, 1=29% Tumour site: colon=88/118, rectum=30/118	To assess the safety and efficacy of bi-weekly irinotecan plus leucovorin-modulated 5-FU intravenous bolus in mCRC according to the age of patients	IRIFAFU given every other week may represent a suitable therapeutic option also for elderly patients with mCRC
Oztop 2004[113]	Single centre Turkey 1993-2002	mCRC Stage: II-IV ≥65	5-FU-based adjuvant chemotherapy (n=51)	Median age: 70 years (65-85) Males: 62.7% ECOG PS: 0=23.5%, 1=56.8%, 2=19.7% [≥70, 0-1=82.8%] Tumour site:	To evaluate the feasibility and tolerability of the adjuvant treatment of elderly patients in early stage CRC	In elderly patients, the use of 5-FU-based adjuvant chemotherapy for CRC was well tolerated, and advanced age is not an obstacle for the adjuvant chemotherapy of CRC

Study	Study details	Population summary	Intervention (n)	Baseline data	Purpose	Author conclusions
				colon=74.5%		
Rosati 2006[116]	Italy Multicentre Follow-up 10.4 months 2004-2005	aCRC Second-line ≥70 years	Irinotecan (CPT-11) (n=23)	Median age: 75 years (70-89) Males: 48% ECOG PS: 0=48%, 1=52% Tumour site: colon=65%	To retrospectively collect data on elderly patients with aCRC responding to defined selection criteria and treated with single-agent CPT as second-line treatment following 5-FU/oxaliplatin-based therapy	A weekly irinotecan administration can induce tumour control in elderly patients with aCRC that has progressed during or shortly after 5-FUl/oxaliplatin-based chemotherapy. However, careful monitoring of haematological toxicity and special instructions to prevent and manage diarrhoea are mandatory in this setting of patients
Bouchahda 2007[102] (abstract only)	France and Spain	mCRC ≥70	Cetuximab with irinotecan (CPT-11) (n=65)	Median age: 77 years (70-84) Males: 66.2% WHO PS: 0=18.5%, 1=61.5%, 2=13.9%, unknown=6.1% Tumour site: colon=73.9%, rectum=21.5%,unknown=4.6%	To explore the tolerability and activity of cetuximab combined with CPT 11 in an unselected population of elderly patients with CPT11-refractory mCRC	The combination of cetuximab with CPT11-based chemotherapy resulted in good activity and acceptable tolerability in elderly patients with heavily pre-treated mCRC, comparable to that of the non-elderly population. This treatment option can be reasonably proposed in this elderly population
Duffour 2010[106]	Single centre France Follow-up 8.3 years 1995-2000	mCRC ≥65=46.6% (≥74=16%)	Intensified 5-FU-based chemotherapy (n=103)	Median age: 70 years (65-80) Males: 58% ≥65 WHO PS: 0=56%, 1=33%, 2=9%, 3=2% <65 WHO PS: 0=67%, 1=29%, 2=4% ≥65 tumour site: colon=79% <65 tumour site:	To verify that older age was not a poor-prognosis variable	Aging did not seem to limit intensified chemotherapy or to affect the pharmacokinetic behaviour of the 5-FU

Study	Study details	Population summary	Intervention (n)	Baseline data	Purpose	Author conclusions
				colon=73%		
Canoui-Poitrine 2011[104] (abstract only)	2007-2010	>70=44.2%	FOLFOX4 (n=86)	Mean age: 65.3±11.5 years Males: 47.7% PS: 0=54.4%	NR	Age was independently associated with FOLFOX4 dose reduction or stop. This can be partly explained by a greater toxicity in elderly for oxaliplatine but not for 5-FU. Among elderly, dependency and impaired mobility may be associated with FOLFOX4 dose reduction or withdrawal
Fornaro 2011[100,107]	Italy 29 months 2004-2009	mCRC Second line=24% Third+=76% ≥70	Cetuximab plus irinotecan (n=54)	Median age=73 years (70-82) Males: 63% ECOG PS: 0=50%, 1=46%, 2=4% Tumour site: colon=76%	To analyse 54 mCRC patients aged ≥70 years who received treatment with cetuximab plus irinotecan after irinotecan failure in order to better define the tolerability of this agent and its efficacy in a subgroup of elderly patients selected according to KRAS and BRAF mutational status	Cetuximab plus irinotecan has a favourable safety profile in elderly mCRC patients, but a reduced dose of irinotecan should be considered. Such a combination can be a useful option for elderly KRAS and BRAF wild-type patients
Kuboki 2011[112]	Single centre Japan Median follow-up 19.5 2005-2008	mCRC Second-line >70	FOLFIRI (n=35)	Median age: 74 years (71-77) Males: 51.4% ECOG PS:0=65.7%, 1=34.3% Tumour site: colon=60%	To analyse retrospectively the efficacy and toxicity in elderly patients (median age, 74 years) treated with second-line FOLFIRI following first-line FOLFOX4 failure	The use of the three active drugs, 5-FU, oxaliplatin and irinotecan, in mCRC produced the longest OS in elderly as well as in younger patients. However, the elderly patients treated with second-line FOLFIRI had a high rate of haematological toxicity. Second-line FOLFIRI may therefore be used

Study	Study details	Population summary	Intervention (n)	Baseline data	Purpose	Author conclusions
						with caution in the elderly
Romano 2011[114] (abstract only)	Italy 2008-2010	Stage: II-III >65	XELOX or FOLFOX (n=31)	Median age: XELOX=71 years FOLFOX=70 years PS: XELOX 0-1=17%, FOLFOX 0-1=77%	Retrospective analysis to verify whether the dose intensity of chemotherapy is administered in routine clinical practice in a consecutive non-selected series of over 65 years patients with resected CRC	Given the convenient oral administration of capecitabine respect to infusional therapy, XELOX is often used in adjuvant setting, but data from large phase III trial indicate that a very large rate of elderly patients withdraw from treatment due to toxicity. Our retrospective analysis in a non-selected series of patients over 65 years confirms that in clinical practice the oxaliplatin planned dose density is rarely administered, so a different schedule (i.e. CAPOX) could be explored in this setting of patients
Khattak 2012[109]	Australia 2006-2010 Funded by Sanofi-Aventis	aCRC First-line ≥70=43%	Single agent fluoropyridimidine Combination chemotherapy (n=951)	Median age: 76 years Males: 62% Tumour site: ≥70: rectum=23% <70: rectum=33%	Assess the impact of age and the choice of initial chemotherapy (single agent vs combination, potentially reflecting age bias) on outcome of patients with mCRC	Treatment outcomes are comparable in both the elderly and younger patients. Patients who received initial combination chemotherapy were younger and had a longer median OS. In our study, age appeared to influence the treatment choices but not necessarily outcome
Twelves 2005[118]	Phase II Multicentre UK, Canada, France, Italy, Spain, Germany,	mCRC First-line ≥65=45.8%	≥65 Capecitabine/oxaliplatin (overall n=96)	Median age: 70 years (65-79) Males: 64%	To analyse data from from the large phase II XELOX study investigating the safety of XELOX as first-line	In the context of an aging population, XELOX provides a highly effective and tolerable first-line treatment for

Study	Study details	Population summary	Intervention (n)	Baseline data	Purpose	Author conclusions
	Israel and Belgium			Median KPS: 90 (80-100) Tumour site: colon=70%, rectum=27%, both=2%	treatment for older patients (>65 years of age) with mCRC	patients with mCRC
			<65 Capecitabine/oxaliplatin	Overall median age: 64 years (34-79) Males: 63% Median KPS: 100 (80-100) Tumour site: colon=58%, rectum=38%, both=4%		
Stec 2010[117]	Single centre Poland 2003-2008	mCRC First-line ≥65	Capecitabine (n=56)	Median age: 73 years (65-83) Males: 67.9% WHO PS:0=31.3%, 1=64.2%, 2=4.4% Tumour site: colon=51.8%, sigmoid=21.4%, rectum=26.8%	A retrospective analysis was conducted to compare the tolerability and efficacy of single-agent capecitabine and FOLFIRI in the first-line treatment of patients aged 65 years with mCRC	Single-agent capecitabine and FOLFIRI are effective first-line regimens in patients aged ≥65 years with mCRC
			FOLFIRI (n=67)	Median age: 68 years (65-80) Males: 61.2% WHO PS: 0=19.6%, 1=60.8%, 2=19.6% Tumour site: colon=29.8%, sigmoid=40.4%, rectum=29.8%		

Study	Study details	Population summary	Intervention (n)	Baseline data	Purpose	Author conclusions
Kim 2013[110,111]	Single centre Korea Follow-up 49.7 months 2003-2010	Stage III ≥65=46.1%	FOLFOX Capecitabine 5-FU/LV UFT/LV (overall n=229)	≥65 median age: 8 years (65-80) Overall median age: 61 years (28-80) ≥65 males: 64.1% <65 males: 56.8% ≥65 ECOG PS: 0-1=97.7%, 2=2.3% <65 ECOG PS: 0-1=99.3%, 2=0.7%	Elderly patients derive similar benefits from 5-FU-based adjuvant chemotherapy in stage III colon cancer; however, conflicting data exist regarding additional benefit from oxaliplatin, fluorouracil and leucovorin (FOLFOX) chemotherapy	Adjuvant oxaliplatin, fluorouracil and leucovorin chemotherapy resulted in similar efficacy without significant increase in toxicity in older patients aged ≥65 when compared with younger patients with curatively resected stage III colon cancer. Therefore, for colon cancer patients aged ≥65, oxaliplatin, fluorouracil and leucovorin chemotherapy can be recommended as safe and effective adjuvant chemotherapy after curative surgery in Asia
Jee 2005[108]	South Korea Median follow-up 19.8 months 2001-2004	aCRC First-line ≥70	Reduced dose of FOLFOX4 (n=20)	Median age: 75 years (70-83) Males: 80% ECOG PS: 1=50%, 2=50% Tumour site: colon=60%	To evaluate the toxicity and efficacy of a reduced dose intensity (mini-) FOLFOX4 regimen as a first-line palliative chemotherapy in elderly patients (≥70 years) with aCRC	The mini-FOLFOX4 regimen was found to be well tolerated with acceptable toxicity, and to provide a benefit for elderly patients with CRC
Ashley 2007[99]	Phase III USA Follow-up 38 months Funded by Pfizer and Sanofi-Aventis	mCRC First-line >70=19.6%	IROX (n=383)	Median age: >70=74 years (71-85) <70=57 years (26-70) Males: >70=39% ≤70=40% ECOG PS: >70: 0-1=96%, 2=5%	The goal of N9741 was to compare time to progression in patients with locally advanced or mCRC (previously untreated for advanced disease) who received FOLFOX or IROX (the experimental regimens), to the	IROX was found to be less active than FOLFOX but with a similar toxicity profile except in patients ages >70 years. Although IROX may be considered in patients intolerant of 5-FU or in patients known to have a dihydropyrimidine

Study	Study details	Population summary	Intervention (n)	Baseline data	Purpose	Author conclusions
				<70: 0-1=94%, 2=6%	control regimen, IFL. This report focuses on the activity and toxicities associated with IROX	dehydrogenase deficiency, it should be used with caution in older patients
Bouchahda 2008[101,103]	Multicentre France Median follow-up 6 2004-2005 Funded by Merck	mCRC Third line+ ≥70	Cetuximab (n=56)	Median age: 76 years (70-84) Males: 59% WHO PS: 0=13%, 1=70%, 2=13%, NA=5% Tumour site: colon=70.4%	The clinical data of consecutive patients aged ≥70 years given cetuximab for mCRC were retrospectively captured from hospital pharmacy registries in seven centres	Cetuximab is safe in an elderly population of heavily pretreated patients. A formal assessment of the benefit/risk ratio of cetuximab in the elderly is warranted from prospective clinical trials using CGA, in order to better define the target subpopulation

aCRC=advanced colorectal cancer; mCRC=metastatic colorectal cancer; 5-FU=fluorouracil; IRIFAFU=irinotecan, 5-FU and folinic acid; LV=leucovorin; FOLFOX=5-FU, oxaliplatin and folinic acid; FOLFIRI=5-FU and irinotecan; XELOX=capeciteabine and oxaliplatin; CAPOX=capecitabine plus oxaliplatin; IFL=irinotecan, 5-FU plus leucovorin; IROX=oxaliplatin and irinotecan; KPS=Karnofsky performance status; ECOG=Eastern Cooperative Oncology Group; WHO=World Health Organisation; PS=performance status; OS=overall survival; ORR=overall response rate; TTP=time to progression; CGA=comprehensive geriatric assessment; NA=not available

10.2 Efficacy evidence

Thirteen studies[100-103,105-113,116-118] reported at least one efficacy outcome of interest. Details can be found in Table 20.

In general, the results across the efficacy outcomes for older and younger patients were similar. PFS/TTP was well reported, the results for older patients ranged from 3 months[112] (TTF) to 21.1 months[109] (PFS). Two studies [110,111,113] presented information regarding 3-year DFS, with rates of 76.5% and 80% for older patients, and rates of 80% and 76.4% for younger patients. Overall survival was fairly well reported, with the lowest OS reported for older patients being 8.3 months,[116] and the highest being 20.7 months.[112] The results for ORR varied, for older patients the lowest reported ORR was 3.3%[112] and the highest was 52%.[118]

Table 20 Efficacy evidence, retrospective studies

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Comella 2003[105]	IRIFAFU	<54: 7.4 55-69: 8.0 >70: 5.3	NR	<54: 13.4 55-69: 15.3 >70: 13.9	NR	<54: 38 55-69: 34 >70: 35	NR
Oztop 2004[113]	5-FU-based adjuvant chemotherapy	3 year DFS: 77.7% ≥70=80% <65=76.4%	NR	NR	NR	NR	NR
Rosati 2006[116]	Irinotecan	TTP: 4.3 (1 to 8)	NR	8.3 (1 to 16)	NR	13	NR
Bouchahda 2007[102] (abstract only)	Cetuximab with irinotecan	4.5 (2.9 to 6)	NR	15 (12 to 17.9)	NR	23	NR
Duffour 2010[106]	Intensified 5-FU-based chemotherapy	NR	NR	≥65: 13.4 (8.8 to 18.4) <65: 18.7 (12.8 to 21.8)	0.154	≥65=35 (22.2 to 50.5) <65=27 (16.1 to 40.9)	p=0.4
Fornaro 2011[100,107]	Cetuximab plus irinotecan	4	NR	11.5	NR	NR	NR
Kuboki 2011[112]	FOLFIRI	TTF 3 (1.2 to 4.7)	NR	20.7 (18.9 to 22.5)	NR	3.3	NR
Khattak 2012[109]	First-line single agent fluoropyridimidine/ combination chemotherapy.	≥70=21.1 <70=21.3	p=0.4	NR	NR	NR	NR
Twelves 2005[118]	XELOX	NR	>65 vs >65 TTP: p>0.85	NR	>65 vs >65 OS: p>0.65	≥65=52 (37 to 68) <65=58 (43 to 71)	NR
Stec 2010[117]	Capecitabine or FOLFIRI	TTP FOLFIRI=8.8 Capecitabine=7.5 ≥70: 9 <70: 7.2	p=0.20 p=0.63	FOLFIRI=19 Capecitabine=15.4	p=0.93	FOLFIRI=28.1 Capecitabine=16.4	p=0.1398

Study	Intervention	Median PFS/TTP (95% CI) Months[a]	Hazard ratio (95% CI)	Median OS (95% CI) Months	Hazard ratio (95% CI)	ORR % (95% CI)	Hazard ratio (95% CI)
Kim 2013[110,111]	FOLFOX4	3-year DFS: ≥65=76.5% <65=80%	p=0.88	3-year OS: ≥65=90.9% <65=92.7%	p=0.98	NR	NR
Jee 2005[108]	FOLFOX4	4.8 (3 to 6.7)	NR	13.5 (11.1 to 16)	NR	43.8 (23.1 to 66.8) [per protocol] 35 (18.1 to 56.7) [intention-to-treat analysis]	NR
Bouchahda 2008[101,103]	Cetuximab	4.5 (2.5 to 6.5)	16 (13.5 to 18.5)	NR	NR	21.4 (10.7 to 32.1)	NR

PFS=progression-free survival; DFS=disease-free survival; TTP=time to disease progression; OS=overall survival; ORR=objective response rates; IRIFAFU=irinotecan, 5-FU and folinic acid; 5-FU=fluorouracil; LV=leucovorin; FOLFIRI=5-FU, leucovorin and irinotecan; XELOX=capeciteabine and oxaliplatin; FOLFOX=5-FU, oxaliplatin and folinic acid/LV; NR=not reported; CI=confidence interval

[a] Values relate to PFS, unless otherwise stated

10.3 Tolerability evidence

Thirteen studies[100-104,106,107,110-118] reported one or more outcome relating to tolerability. Details are presented in Table 21.

Although several studies presented data for the median number of cycles per patient, dose intensity was not well reported. Oztop et al[113] reported a median RDI of 92%, and Kim et al[110,111] reported a statistically significant difference between older and younger patients (75% vs 80%; p=0.009). Duffour et al[106] reported the number of patients who received six cycles or more, and there was no statistically significant difference between older and younger patients (87.5% vs 84%; p=0.58).

The most commonly reported reasons for discontinuation or withdrawal of treatment were disease progression and AEs. Where comparisons were made between older and younger patients, the results were similar. Dose modifications and interruptions were fairly well reported. Kim et al[110,111] reported that chemotherapy delays were more frequent in the younger patients than in the older patients (69% vs 65.5%; p=0.08).

Common non-haematological AEs included diarrhoea and skin rash. Studies also reported neutropenia and leukopenia as common haematological AEs. Romiti et al[115] found no specific relationship between age and AEs, and Duffour et al[106] reported no statistically significant difference between age groups. Canoui-Poitrine et al[104] did report a statistically significant difference for neurotoxicity related to oxaliplatin between older and younger patients (46.4% vs 14.3%; p=0.003).

Table 21 Tolerability evidence, retrospective studies

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Romiti 2002[115]	Raltitrexed Median cycles per patient=6 (1-10) ≥70=6 (1-9) <70=5 (1-10)	NR	Toxicity-related dose reduction: ≥70=10% <70=15% Therapy delay: ≥70=36% <70=37%	Grade 3-4: ≥70 Asthenia=12% Diarrhoea=10% <70 Asthenia=0% (p=0.03) Diarrhoea=5% (p=0.29) No specific relationship between age and toxicity. Treatment-related deaths=3
Oztop 2004[113]	5-FU-based adjuvant chemotherapy Median RDI=92%	NR	Dose reduction=7.8% due to haematological toxicity Interrupted=1 patient	Grade 3-4 toxicities: Myelosuppression=17.6% Diarrhoea=15.6%
Rosati 2006[116]	Irinotecan Median cycles per patient=4 (1-8)	Withdrawals after ≤2 cycles due to: Disease progression=4 (17.3%) AEs=2 (8.6%)	Delay=16 cycles (14%) [mainly due to neutropenia] Dose reduction=5 patients (21.7%) [mainly due to neutropenia]	Grade 3 diarrhoea=13% Grade 3 neutropenia=30.4% Grade 4 neutropenia=8.6%
Bouchahda 2007[102] (abstract only)	NR	NR	NR	Cetuximab with irinotecan (CPT-11) Grade 3 acneiform skin rash=13% Grade 3 diarrhoea=16% (Grade 4=3%)
Bouchahda 2008[101,103]	Cetuximab Median cycles per patient=8 (1-34) Responding patients median weekly doses=20.5 (5-34) Stable patients median weekly dose=10 (4-20)	89% discontinued due to: Disease progression=80% Toxicity=12%	NR	Grade 3 skin rash=11% Grade 3-4 diarrhoea=20%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Duffour 2010[106]	Intensified 5-FU-based chemotherapy At least 6 cycles; ≥65=87.5% <65=84% p=0.58	Discontinuation; ≥65=12.5% <65=14.6% Due to: Severe toxicity=4 patients Disease progression=5 patients Toxicity and progression=3 patients Refusal=1 patient Haemorrhage (severe adverse avent)=1 patient	5-FU dose increase: ≥65=83% <65=78% (p=0.509) [Dose increase of ≥100% in 50% of both ≥65 and <65 age groups]	Any grade 3-4 toxicity: ≥65=33.3% <65=34.5% (p=0.9) Neutropenia: ≥65=10% <65=17%
Canoui-Poitrine 2011[104] (abstract only)	NR	NR	Dose reduction/stop within 3 months: FOLFOX4=48.4% (35.6-63) 5-FU=26.7% (12-44.8) Oxaliplatin=47.2%(37-61) Associated with age (≥70) p=0.007 Mainly due to neurotoxicity and haematotoxicity	Neurotoxicity related to oxaliplatin: ≥70=46.4% <70=14.3% (p=0.003)
Fornaro 2011[100,107]	NR	Cetuximab plus irinotecan: Discontinuations: Disease progression=81% Toxicity=2% Refusal=4% Local procedures=4%	Does reduction required in 39% of patients	Grade 3 diarrhoea=17% Grade 3 skin rash=15%
Kuboki 2011[112]	FOLFIRI Median cycles per patient=5 (2-37)	Discontinuation: Non-progression of disease=29% Interstitial lung disease=5.7% Febrile neutropenia=2 pts Treatment-related death=1	Dose reduction=26% (78% due to haematological toxicity)	Neutropenia=71.4% Leukopenia=45.7% Febrile neutropenia 11.4%

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
		patient (14% of which discontinued before first evaluation)		
Romano 2011[114] (abstract only)	NR	Toxicity-related withdrawals: XELOX=32% FOLFOX=18%	Median cycle delay: XELOX=18% FOLFOX=15%	Grade 3-4: XELOX Neutropenia=19% Thrombocytopenia=26% Neuropathy=26% FOLFOX Neutropenia=16% Thrombocytopenia=18% Neuropathy=16%
Twelves 2005[118]	XELOX Median cycles per patient=8 (1-26)	Withdrawals Total: ≥65=59% <65=63% Adverse events: ≥65=14% <65=19% Death: ≥65=7% <65=0% Insufficient response: ≥65=36% <65=37% Other: ≥65=2% <65=8%	XELOX dose reduction: ≥65=27% <65=19% Only capecitabine dose reduction: ≥65=14% <65=15% Only oxaliplatin dose reduction: ≥65=11% <65=13%	NR

Study	Treatment received and/or dose intensity	Discontinuations and/or withdrawals	Dose modifications and/or interruptions	Proportion of patients with grade 3-4 adverse events
Stec 2010[117]	Capecitabine or FOLFIRI Median cycles per patient: Capecitabine=7 (1-32) FOLFIRI=10.5 (1-28)	NR	NR	Grade 3 toxicities FOLFIRI: Neutropenia=11.9% Asthenia=13.4% Hand-foot=0% Capecitabine: Neutropenia=3.6% Asthenia=8.9% Hand-foot=19.6%
Kim 2013[110,111]	FOLFOX4 Median cycles per patient: ≥65=11 <65=11.5 RDI Oxilaplatin: ≥65=0.76 <65=0.79 5-FU: ≥65=0.75 <65=0.80 (p=0.009)	Planned 12 cycles: ≥65=81.6% <65=89.4%	Delayed chemotherapy: ≥65=65.5% <65=69% (p=0.08)	Grade 3-4 neutropenia: ≥65=62.1% <65=46.5% (p=0.02)

RDI=relative dose intensity; AE=adverse event; 5-FI=5-fluorouracil; FOLFOX=5-FU, oxaliplatin and leucovorin;FOLFIRI=5-FU, leucovorin and irinotecan; XELOX=capeciteabine and oxaliplatin; NR=not reported

10.4 Comprehensive geriatric assessment and quality of life

None of the included studies reported QoL or CGA outcomes.

10.5 Discussion

Heterogeneity and lack of methodological quality of the included retrospective studies mean that useful comparison across studies and outcomes was not possible. The data from retrospective studies are difficult to interpret in any meaningful way; however, the data have been included for completeness to show the size of the evidence base and for reference. It should be noted that although retrospective evidence is not ranked as highly as evidence derived from RCTs, many of the retrospective studies included patients who more closely reflect patients seen in routine clinical practice.

11 DISCUSSION

The WHO[8] states that most countries of the developed world use the chronological age of 65 years to define 'elderly' or 'older' populations, whereas the British Geriatrics Society[9] describes geriatric medicine as being mainly concerned with people aged over 75. As expected, one of the key findings of this review is that there is no commonly used definition describing the age (or age range) of 'older' patients who participate in CRC studies. The age of patients described as 'older' ranged from over 60 years to over 75 years across the included studies.

Despite the fact that CRC mainly affects older people, and incidence increases with age, there is a lack of good-quality RCT evidence relating to solely older patients with CRC. Data from the included RCTs are not generalisable to the older population, as strict patient selection processes ensure that patients with CRC who are recruited to RCTs are generally fitter and healthier than patients seen in routine clinical practice. However, data may be generalisable to the subgroup of older patients with CRC seen in routine clinical practice who are generally fit and healthy. The non-RCT evidence collated in this review is derived predominantly from single cohort and retrospective studies, which were generally small and of poor methodological quality. Many studies did not fully present information relating to study characteristics and study populations.

Efficacy outcomes were well reported across the study types, and results show that, in general, older patients with CRC gain survival benefit and respond to treatment with chemotherapy. Where comparisons were made between older and younger patients, there is some evidence that older patients often achieve similar results to their younger counterparts. Data relating to tolerability outcomes were generally well reported, and show that overall, many older people can tolerate chemotherapy. However, some older patients received fewer cycles of treatment or experienced higher rates of treatment discontinuation, withdrawal and treatment delays compared with younger patients. In addition, some studies showed slightly increased AEs for older patients, which is a clear concern for clinicians and patients when deciding between treatment options.

The use of QoL measures was infrequently reported across all study types, which makes it difficult to draw firm conclusions for older people who are treated for CRC. This review highlights that there is no standard format for collecting and/or reporting QoL data in CRC trials; this is unfortunate, as access to robust QoL data is required when healthcare professionals consider treatments for patients with CRC. There were limited data reported on the use of CGA tools across studies, either as criteria for study entry or as an outcome measure alongside other measures such as QoL. All information relating to a patient's potential well-being and response to therapy is important when making treatment decisions, as clinicians and multidisciplinary teams need to take into account patients'

comorbidities and fitness levels; this is not reflected in the studies, which lack appropriate and standardised tools and measures.

11.1 Strengths and limitations of the assessment

One of the main strengths of this review is that it combines evidence from a wide range of studies to create a comprehensive evidence base that describes how older patients with CRC are treated in clinical studies. However, the inclusion criteria employed in this review were deliberately broad, and led to the inclusion of diverse study populations, which often differed in terms of disease stage and histology, treatment type and line of treatment. As there is considerable heterogeneity, it was not possible to make firm conclusions for specific subgroups of older patients with CRC.

The overall methodological quality of the included studies was poor, and therefore, the results must be viewed with caution. Some of the studies selected fitter, healthier patients and the results are not necessarily generalisable to the population of older people seen in routine clinical practice.

The review focusses on the extent to which older patients with CRC can tolerate chemotherapy and it is anticipated that the data collected will help clinicians to make informed decisions about how to treat older patients with this disease. Using the data available, it has been possible to make some comparisons between older and younger patients, which will help to indicate how useful chemotherapy is in clinical practice for this specific patient population.

There was great variability across studies in terms of how well outcome measures were utilised and reported. The interpretation of the available data on tolerability outcomes was difficult to synthesis and interpret, and there were very little data reported on QoL and CGA.

Although the results of this review highlight that chemotherapy may be a viable treatment option for older people with CRC, it should be noted that any conclusions drawn are not treatment recommendations; the evidence should instead be used to enable clinicians and patients to have meaningful discussions about treatment options.

12 CONCLUSIONS

There is a distinct lack of good-quality research into the treatment of older patients with CRC. Chemotherapy may be effective in treating older patients with CRC, and although older patients are at greater risk of AEs, treatment with chemotherapy appears to be tolerable. Treatment should not routinely be withheld from older patients, and older patients should be given the opportunity to discuss treatment options with healthcare professionals, taking into account factors such as fitness, comorbidities and personal choice.

12.1 Suggested research priorities

This review has highlighted that chemotherapy may be clinically effective in older people with CRC, and there is scope for trials to be conducted on solely older populations in order to fully ascertain the benefits and potential harms of treatment in this population. It would be useful for future trials to explore the possibility of reducing the dose for patient groups who might be disadvantaged by the potential side-effects of chemotherapy treatment.

It is essential that future research adopts more uniform definitions and standardised assessment tools that measure outcomes objectively. Outcomes should also be reported consistently to enable meaningful synthesis of data, so that each study adds valuable information to the evidence base.

Future trials could make more use of structured, standardised CGA assessments as part of their inclusion criteria; it is possible that the lack of use of CGA tools in clinical practice in the UK is due to the limited research available to support their use.

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14 APPENDICES

Appendix 1: Literature search strategies

Elderly Cancer Search History (35 searches)
Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) 1946 to Present with Daily Update

# ▲	Searches	Results
1	exp Breast Neoplasms/	206832
2	(breast$ adj5 (neoplasm$or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	57204
3	exp Colorectal Neoplasms/	139935
4	(colorectal adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	63395
5	exp Lung Neoplasms/	165165
6	(lung adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	116112
7	exp Carcinoma, Renal Cell/	20951
8	((renal cell or kidney) adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	21641
9	exp Leukemia, Myelogenous, Chronic, BCR-ABL Positive/ or exp Leukemia, Myeloid, Chronic-Phase/ or exp Leukemia, Myeloid, Chronic, Atypical, BCR-ABL Negative/	15723
10	(chronic myel$ adj2 leuk?emia).ti,ab.	19580
11	exp Lymphoma, Non-Hodgkin/	80985
12	(Lymphoma$ adj5 (non-hodgkin$ or non hodgkin$)).ti,ab.	28219
13	or/1-12	663599
14	*"Aged, 80 and over"/ or *Aged/	21737
15	(senil$ or geriatr$ or older or elder$ or late-life or later-life or late$ life).ti,ab.	392827
16	14 or 15	401572
17	13 and 16	15012
18	chemotherap$.tw. or drug therapy.fs.	1734499
19	(adjuvant adj5 chemotherap$).tw.	17651
20	exp Antineoplastic Agents/ or exp Antineoplastic Combined Chemotherapy Protocols/ or exp Chemotherapy, Adjuvant/	821443
21	or/18-20	2172920
22	exp Medication Adherence/ or adherence.tw.	58141
23	(survival adj benefit$).tw.	7695
24	(recurrence risk$ or relapse-free survival).tw.	6612
25	exp Drug Toxicity/ or exp Drug Tolerance/ or exp Safety/ or exp Treatment Outcome/ or exp Disease-Free Survival/	719437
26	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).tw.	208607
27	(side effect$ or undesirable effect$ or treatment-emergent or treatment-related or tolerability or safety or toxic effect$ or dose intensity or toxicity).tw.	617560
28	(clinical adj5 (effectiveness or efficacy or effect$ or benefit$)).tw.	113247
29	exp "Quality of Life"/ or (quality of life or qol).tw.	164254
30	or/22-29	1568681
31	21 and 30	520864
32	17 and 31	2926
33	(animals not (humans and animals)).sh.	3760147
34	32 not 33	2924
35	**limit 34 to (english language and yr="2000 -2013")**	2146

EMBASE Search History (33 searches)
Embase 1974 to 2013 May 24

# ▲	Searches	Results
1	exp breast cancer/	258454
2	(breast$ adj5 (neoplasm$or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	75564
3	exp colon carcinoma/ or exp colon cancer/ or exp colorectal cancer/ or exp rectum cancer/ or exp rectum carcinoma/	158617
4	(colorectal adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	89748
5	exp lung tumor/ or exp lung cancer/	241425
6	(lung adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	160685
7	exp kidney cancer/	65356
8	((renal or kidney) adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$)).ti,ab.	62964
9	exp chronic myeloid leukemia/	28802
10	(chronic myel$ adj2 leuk?emia).ti,ab.	24827
11	exp nonhodgkin lymphoma/	116117
12	(Lymphoma$ adj5 (non-hodgkin$ or non hodgkin$)).ti,ab.	37418
13	or/1-12	878499
14	exp geriatric patient/ or *aged/	50605
15	(senil$ or geriatr$ or older or elder$ or late-life or later-life or late$ life).ti,ab.	531929
16	14 or 15	546878
17	13 and 16	22973
18	chemotherap$.tw.	353300
19	(adjuvant adj5 chemotherap$).tw.	26741
20	exp antineoplastic agent/ or exp consolidation chemotherapy/ or exp multimodal chemotherapy/ or chemotherapy/ or exp induction chemotherapy/ or exp cancer combination chemotherapy/ or exp maintenance chemotherapy/ or exp cancer chemotherapy/ or exp adjuvant chemotherapy/ or exp combination chemotherapy/	1462883
21	or/18-20	1546201
22	(clinical adj5 (effectiveness or efficacy or effect$ or benefit$)).tw.	165108
23	*patient compliance/ or adherence.tw.	149576
24	(survival adj benefit$).tw.	12002
25	(recurrence risk$ or relapse-free survival).tw.	9402
26	exp drug toxicity/ or exp drug tolerance/ or exp drug safety/ or exp treatment outcome/ or exp disease free survival/	1218587
27	(adverse adj2 (effect or effects or reaction or reactions or event or events or outcome or outcomes)).tw.	311356
28	(side effect$ or undesirable effect$ or treatment-emergent or treatment-related or tolerability or safety or toxic effect$ or dose intensity or toxicity).tw.	886887
29	exp "quality of life"/ or (quality of life or qol).tw.	277356
30	or/22-29	2407159
31	21 and 30	418422
32	17 and 31	5575
33	**limit 32 to (human and english language and yr="2000 - 2013")**	**4047**

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Search History

[Breast Neoplasms] explode all trees 7763
breast cancer* or breast neoplasm* or breast tumour* or breast carcinoma*:ti,ab,kw (Word variations have been searched) 14703
[Colorectal Neoplasms] explode all trees 4628
"colorectal cancer":ti,ab,kw (Word variations have been searched) 4311
[Lung Neoplasms] explode all trees 4272
"lung cancer":ti,ab,kw (Word variations have been searched) 6836
[Carcinoma, Renal Cell] explode all trees 419
kidney cancer or renal cell cancer:ti,ab,kw (Word variations have been searched) 789
[Leukemia, Myelogenous, Chronic, BCR-ABL Positive] explode all trees 304
"chronic myeloid leukaemia":ti,ab,kw (Word variations have been searched) 101
[Lymphoma, Non-Hodgkin] explode all trees 1136
non-hodgkin's lymphoma:ti,ab,kw (Word variations have been searched) 1203
#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 30561
(senil* or geriatr* or older or elder* or late-life or later-life or late*):ti,ab,kw (Word variations have been searched) 67255
Aged] explode all trees 554
#14 or #15 67394
#13 and #16 2332
(chemotherap* or drug therap*):ti,ab,kw (Word variations have been searched) 111982
MeSH descriptor: [Drug Therapy] explode all trees 108765
#18 or #19 173119
#17 and #20 1068

Web of Knowledge

Results:
Topic=(breast cancer* or colorectal cancer* or renal cell carcinoma* or chronic myeloid leukemia* or non-hodgkin lymphoma*) AND Topic=(chemotherap* or Bevacizumab or Avastin or Cetuximab or Erbitux or Everolimus or Afinitor or Fulvestrant or Faslodex or Lapatinib or Tyverb or Bendamustine or Levact or Bortezomib or Velcade or Rituximab or Mabthera or Rituxan) AND Topic=(aged or senil* or geriatr* or older or elder*)

Refined by: Languages=(ENGLISH) AND Web of Science Categories=(ONCOLOGY OR HEMATOLOGY) AND Document Types=(PROCEEDINGS PAPER OR MEETING ABSTRACT) AND Research Areas=(ONCOLOGY OR HEMATOLOGY)

Timespan=2000-01-01 - 2013-02-03. Databases=Conference Proceedings Citation Index-Science (CPCI-S).

Appendix 2: Quality assessment

The quality of RCTs will be assessed using criteria based on CRD[10] guidance:

- Was the method used to assign participants to the treatment groups really random?*
- Was the allocation of treatment concealed?**
- Was the number of participants who were randomised stated?
- Were details of baseline comparability presented in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Was baseline comparability achieved in terms of treatment-free interval, disease bulk, number of previous regimens, age, histology and performance status?
- Were the eligibility criteria for study entry specified?
- Were any co-interventions identified that may influence the outcomes for each group?
- Were the outcome assessors blinded to the treatment allocation?
- Were the individuals who administered the intervention blinded to the treatment allocation?
- Were the participants who received the intervention blinded to the treatment allocation?
- Was the success of the blinding procedure assessed?
- Were at least 80% of the participants originally included in the randomisation process followed up in the final analysis?
- Were the reasons for withdrawals stated?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Was an intention-to-treat analysis included?
- Was the study sufficiently powered for the primary outcome(s)?

**(Computer-generated random numbers and random number tables will be accepted as adequate, while inadequate approaches will include the use of alternation, case record numbers, birth dates and days of the week)*

*** (Concealment will be deemed adequate where randomisation is centralised or pharmacy-controlled, or where the following are used: serially numbered identical containers, on-site computer based systems where the randomisation sequence is unreadable until after allocation, other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients. Inadequate approaches will include: the use of alternation, case record numbers, days of the week, open random number lists and serially numbered envelopes even if opaque).*

Items will be graded in terms of ✓ yes (item properly addressed), ✗ no (item not properly addressed), ✓/✗ partially (item partially addressed), **?** Unclear/not enough information, or **NA** not applicable

Appendix 3: Table of excluded studies with rationale

Study	Reason for exclusion	Study	Reason for exclusion
Anon 2006[119]	no outcomes	Howard 2010[120]	study design
Abraham 2013[121]	no outcomes	Hsiao 2011[122]	no outcomes
Arora 2003[123]	comparator	Howard 2010[120]	study design
Aschele 2002[124]	population	Ibrahm 2004[125]	population
Assy 2012[126]	population	Jansen 2011[127]	study design
Bailey 2003[128]	no outcomes	Jehn 2011[129]	no outcomes
Basdanis 2004[130]	no outcomes	Kahn 2010[131]	study design
Beretta 2002[132]	no outcomes	Koo 2008[133]	population
Berger 2005[134]	population	Mantello 2005[135]	treatment
Bittoni 2010[136]	age unclear	Margalit 2011[137]	chemoradiation
Blanke 2011[138]	treatment	Marquardt 2011[139]	insufficient data
Boudreault 2011[140]	no outcomes	Mathieson 2010[141]	study design
Bouvier 2008[142]	treatment	Morelli 2007[143]	resection
Cafiero 2003[144]	treatment	Nannini 2009[145]	study design
Carrato 2007[146]	population	Nogué 2005[147]	no outcomes
Cen 2012[148]	no results	Oba 2011[149]	protocol only
Cheung 2012[150]	no outcomes	Obiedat 2009[151]	treatment
Comella 2005[152]	no outcomes	Papamichael 2008[153]	study design
Copur 2009[154]	population	Pasetto 2006[155]	no outcomes
Damianovich 2007[156]	no outcomes	Price 2010[157]	letter to editor
Dharma-Wardene 2002[158]	no outcomes	Ramsdale 2012[159]	outcomes
Diaz 2006[160]	no outcomes	Riggs 2012[161]	population
Djedi 2012[162]	no outcomes	Riggs 2012[163]	population
Fata 2002[164]	Insufficient data	Sacco 2007[165]	no outcomes
Folprecht 2006[166]	no outcomes	Sanoff 2007[167]	study design
Franchi 2003[168]	case series	Sanoff 2012[169]	no outcomes
Francois 2011[170]	no data shown for >65s	Sargent 2001[171]	treatment/comparator
Garcia-Alfonso 2009[172]	no data shown for >65s	Sargent 2001[171]	no outcomes
Gil 2004[173]	no data shown for >65s	Sato 2011[174]	population
Glehen 2004[175]	treatment	Seymour 2007[176]	no outcomes
Goldschmidt 2004[177]	opinion/case report	Seymour 2011[178]	population
Gruenberger 2005[179]	surgery alone arm	Shankaran 2012[180]	no outcomes
Guetz 2009[181]	treatment	Tournigand 2006[182]	no outcomes
Hartmann 2004[183]	no results	Townsend 2010[184]	no outcomes
Henry 2008[185]	no results	Wellington 2001[186]	not trial
Heras 2007[187]	no baseline data	Wildes 2009[188]	no outcomes
Ho 2005[189]	study design	Yoshida 2012[190]	population
Hofheinz 2005[191]	population	Zafar 2009[192]	population