Treatment of older patients with colorectal cancer: a perspective review

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***Abstract*:** In a continuously aging population, the burden of colorectal cancer (CRC) is rising among older patients. Despite the fact that almost half of the cases occur in patients over 75 years, this age group is subjected to disparities regarding diagnostic and therapeutic options. So far, exclusion of older patients from randomized clinical trials has resulted in a lack of evidence-based guidelines. Nevertheless, newer data from studies specifically targeting older patients and subgroup analyses indicate that proper treatment planning and specific medical and geriatric assessment can achieve a safe and beneficial treatment result in older patients, often with similar outcomes to their younger counterparts. Resection of the primary tumour, if feasible, should be the primary goal of surgery aiming for cure, although it should be avoided under emergency conditions. Chronological age *per se* should not be an exclusion criterion for adjuvant or palliative chemotherapy, or targeted therapies. Careful patient selection, dose adjustments, close monitoring and early intervention in the event of side effects are essential. The benefits of treatment must be balanced with potential effects of treatment and patients' wishes.

Keywords: chemotherapy, colorectal cancer, elderly, geriatric, surgical management

Introduction

Colorectal cancer (CRC) is the third commonest cancer in men, accounting for about 663,000 new cases worldwide every year and the second commonest in women, with around 571,000 new cases worldwide every year, based on World Health Organization GLOBACAN data. Eight percent of all cancer deaths are attributed to colon cancer, placing it fourth in the rank for cancer-related death causes. About 608,000 deaths are estimated each year from CRC worldwide [GLOBACAN, 2008].

The burden of cancer in the US population is expected to rise sharply over the next two decades [Smith *et al*. 2009]. It is estimated that the overall cancer incidence will increase by 45% by 2030 (from 1.6 million in 2010 to 2.3 million in 2030), with the greatest increase borne by older patients and minorities. More specifically, a 67% increase in cancer incidence is anticipated for older adults compared with an 11% increase for younger adults. By 2030, approximately 70% of all cancers will be diagnosed in older adults. Europe carries a significant load of the global burden, with one-quarter of the cases diagnosed worldwide observed in Europe (in 2008) despite the fact that it comprises only one-ninth of the world's population [Ferlay *et al.* 2013]. Age is a major risk factor for CRC. The incidence increases with age, with a median age of diagnosis at about 70 years. Approximately 70% of cases develop over the age of 65, and 40% of patients in total are 75 years or older, as calculated by the SEER database (http://seer.cancer.gov/csr/1975_2006). Despite a substantial improvement in survival in patients under 75 years with CRC, especially those with stage III disease, probably due to increased chemotherapy administration [van Steenbergen *et al.* 2010], the survival rate of older patients still remains low, reflecting the disparities in diagnosing and treating CRC in the older population.

Comparing and analyzing differences in survival between older (70–84 years) and middle-aged patients with cancer (55–69 years) based on the data obtained from the EUROCARE project, it was shown that significant survival improvement was observed from 1988 to 1999 for all cancer

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sites except cervical cancer. However, survival increased at a slower rate in the older population, so that the gap between younger and older patients widened. Most of this age gap was due to a very large difference in survival after the first year following the diagnosis. The relative excess of death 1 and 5 years after diagnosis for patients with CRC was 1.76 for the older group and 1.3 for the middle-aged group in women, and 1.47 and 1.11 in men respectively [Quaglia *et al.* 2009]. The underlying cause of this gap is multifactorial, since this age group is subjected to many biological differentiation features as well as socioeconomic effects. Limited access to healthcare facilities, low-level social support, limited referrals to specialists and degenerative biological issues (comorbidities, renal impairment, cognitive function impairment), which lead to inability to undertake treatment, all influence management and furthermore the statistics.

It is worth noting that, for older patients who survive the first year, their prognosis approaches that of middle-aged patients. Therefore, distinguishing the frail older patients from those with a good health status could potentially identify those who might benefit from intensive therapy. It has also been noted that survival rates of older American patients are better than those of their European counterparts. The age-standardized mortality rate for the period 1998–2005 in patients with CRC aged over 40 was 208.5 for European patients (Italy) compared with 158.7 for the US population for men, and 116 and 112 for women respectively [Quaglia *et al.* 2013]. The differences in survival between Europe and the USA can be attributed to earlier diagnosis, affecting the stage of disease [Ciccolallo *et al.* 2005]. The fact that older patients in the USA were more likely to have surgery and adjuvant chemotherapy compared with Europeans may also have contributed to improved survival rates [Allemani *et al.* 2013].

Despite the disproportionate burden of CRC cases and high mortality rates in older patients, the evidence-based data for treatment are lacking due to low representation of this age group in clinical trials. In a recent review of 109 phase II and III clinical trials that were published in major medical journals in 2007, 20.2% used an upper age limit exclusion criterion, and only 38.5% of the trials performed an age-specific subgroup analysis [Zulman *et al.* 2011]. In a single-centre retrospective European cohort study that included 110 patients with CRC over 75 years of age, 96 were surgically treated but only 6 of 23 with stage III disease received adjuvant treatment, only 3 of 18 with stage IV disease received palliative chemotherapy and 4 of 14 were treated with adjuvant radiotherapy for rectal cancer [Aparicio *et al.* 2009].

From the total number of patients recruited in the two major adjuvant clinical trials who demonstrated the efficacy of oxaliplatin, MOSAIC and NSABP, less than 1% and 5% respectively were over 75 years of age [Sanoff *et al.* 2012b].

Surgery

Patients with stage I–III disease are candidates for surgical resection, aiming to provide cure and remains the first treatment option. Selected patients with stage IV disease may also benefit. The majority of patients with stage I or II disease are cured by surgery alone. In a European population study the proportion of patients resected with curative intent rose from 71.7% to 77.9% for patients under 75 years compared with the period 1976–1987 and 1989–1999 and from 57.5% to 72.1% in older patients [Mitry *et al.* 2005]. The increase in resection rate, coupled with more aggressive surgical approaches concerning local and distant disease, along with the decrease in postoperative mortality can go some way towards explaining the improved survival of patients with CRC [Mitry *et al.* 2005]. However, in a registry-based study including 6457 patients from the Rotterdam Cancer Registry, an increase in the incidence of postoperative mortality was associated with advancing age. The postoperative mortality rate increased from 1% for younger patients under 60 years of age to 10% for patients over 80 years [Damhuis *et al.* 1996].

The question whether geriatric patients benefit from surgery with curative intent has been addressed through retrospective reviews. In a more recent study that compared perioperative and long-term outcomes following colorectal surgery in patients aged 55–75 years and over 75 years in a single centre from 1998 to 2008, it was shown that the operative mortality rate was 5.9% in the older group and 2.1% in the younger group. The 3-year, 5-year and 10-year survival rates were 37%, 16.2% and 5.1% in the older group and 52.3%, 35.1% and 24.7% in the younger group respectively [Fontani *et al.* 2011]. More deaths unrelated to cancer were found in the older group, while cancer-specific mortality

was similar between groups. Perioperative supportive measures such as aggressive respiratory support for preventing pneumonias should be encouraged. A scoring tool for assessing postoperative mortality risk has been suggested by the American Society of Anesthesiology. This includes age, disease stage and urgency of surgery as risk factors. The excess mortality of older people can be attributed to increased mortality during the first year [Audisio and Papamichael, 2012]. Mortality at year 1 post surgery exceeds 50% in patients over 80 years old, while mortality rate at 1 month post surgery is 31%. This is usually due to cardiorespiratory complications. In general, however, older patients have an acceptable perioperative morbidity, mortality and survival rate compared with their younger counterparts, so age alone should not be a factor for not going ahead with surgery [Fontani *et al.* 2011]. Around 40% of older patients present as emergencies with obstruction or perforation, leading to higher rates of palliative surgery [Audisio *et al.* 2004]. The presence of obstruction or perforation also triples the perioperative mortality rate in older patients. Therefore, emergency surgery should be avoided at all costs. A diverting stoma is performed more readily by the surgeon in an older patient compared with a younger one, and the possibility for a reversal later on is as low as 50% [Zbar *et al.* 2012]. Minimally invasive techniques, such as laparascopic surgery, may be of benefit to older patients as they result in shorter admission duration, earlier recovery, less pain, and ultimately less mortality and morbidity rates, with the presupposition that these are performed by surgeons experienced in the technique. In terms of temporary relief of obstruction to avoid emergency surgery, self-expandable metal stents can be used [Lee *et al.* 2013]. In this way, various clinical parameters that affect the operational outcome, such as anaemia, dehydration, electrolyte imbalance and nutritional status, can be corrected. A planned anaesthetic assessment and adjustments in medication are also crucial for the outcome of the surgery. In a recent review it was found that the primary anastomosis rate was significantly higher in the stented group compared with the emergency surgery group with a lower overall stoma rate, and no increase in the risk of anastomotic leak or intra-abdominal abscess [Cirocchi *et al.* 2013]. In general, the resolution of the obstruction is the primary goal in an emergency situation, and the resection of the bowel should be postponed to a later stage. If urgent surgery cannot be postponed, the least traumatic procedure should be chosen.

Rectal surgery is technically more demanding than colectomies. Total mesorectal excision (TME) is considered the standard treatment for rectal cancer. It is a major visceral surgery, with complications far more severe and life threatening in older patients compared with younger ones [Rutten *et al.* 2008]. For example, anastomotic leakage which occurs at the same rate both in older and younger patients results in excessive mortality of the former compared with the latter (57% *versus* 8.2%). It is worth noting that, as reported in the Dutch TME study, older patients with rectal cancer who were not randomized in the neoadjuvant radiation arm had worse cancer-specific mortality rates compared with those who received standard treatment. This information suggests that older patients respond to neoadjuvant treatment. Nevertheless, noncancer-related mortality seems to be higher in older patients with rectal cancer who receive preoperative radiation compared with those who undergo surgery alone [Rutten *et al.* 2007]. Although local recurrences developed less frequently in patients treated with preoperative radiotherapy compared with surgery alone, the postoperative complications such as pelvic abscess or anastomotic leakage are more common in patients who have received radiation treatment [Maas *et al.* 2013]. Overall, omitting preoperative radiation in older patients may be justified since it does not seem to provide a substantial survival benefit and can result in postoperative complications.

Adjuvant therapy

The use of adjuvant chemotherapy has place in stage III and perhaps high-risk stage II disease with the aim of eradicating any micrometastatic residual disease following surgery. Despite concerns about toxicity in patients over 75 years of age, adjuvant treatment seems to provide benefit both in terms of disease-free survival (DFS) and overall survival (OS). However, the actual survival gain may be difficult to assess in older patients, as these patients have an increased death rate from noncancer causes.

A recent retrospective review was performed to assess the effect of adjuvant chemotherapy in patients with stage III disease who were diagnosed after age 75. Data were collected from four major data sources (SEER-Medicare, NYSCR,

NCCN outcomes database, CanCORS). A total of 5489 patients diagnosed from 2004 to 2007 were included in the analysis [Sanoff *et al.* 2012b]. The investigation aimed to compare two main treatment strategies: chemotherapy *versus* no chemotherapy; in addition, the treatment subsets of oxaliplatin-containing *versus* nonoxaliplatin groups were looked at. Survival for the chemotherapy-treated patients was substantially better and the survival benefit was comparable to that previously demonstrated in randomized trials. The use of oxaliplatin only added an incremental survival benefit again similar to randomized trials. Quality of life (QOL) could not be assessed.

More recently, the ACCENT group obtained and analyzed data from seven phase III adjuvant trials that compared single agent fluoropyrimidines with combination regimens in terms of DFS, OS and time to recurrence (TTR). From a total number of 14,528 patients, 2575 were older than 70 years. One of the conclusions from this analysis was that oral fluopyrimidines provide a similar benefit to intravenous 5 fluorouracil (5FU) regardless of age. Regarding combination regimens, older patients did not benefit from the addition of irinotecan to 5FU. The assessment for efficacy of oxaliplatin, however, did not provide very clear answers. The addition of oxaliplatin provided a short-term reduction in the risk of recurrence, but after a period of time the OS benefit diminished as older patients died from other causes. It is therefore unclear as to which subset of older patients may derive benefit from oxaliplatin-based regimens [McCleary *et al.* 2013]. Unfortunately, the ACCENT analysis has a number of limitations, as it lacks toxicity, dose intensity and comorbidity data. Individual clinical decision making after careful assessment and consideration may therefore be a more appropriate approach for fit older patients as regards the use of oxaliplatin-based therapy.

The administration of adjuvant chemotherapy in patients with stage II disease is controversial at best. Treatment decisions for older patients are even more difficult. In a recent subgroup analysis of the MOSAIC study of 315 patients aged 70–75 with stage II disease who were randomly assigned to receive either FOLFOX (folinic acid, FU, oxaliplatin) or FU/leucovorin (FL), it was shown that treatment with FOLFOX did not improve DFS, TTR or OS compared with the standard arm [Tournigand *et al.* 2012]. Nevertheless, the sample of patients was small and restricted to patients aged under 76 years.

Despite the fact that trials demonstrated the benefit of adjuvant single-agent fluoropyrimidine in this age group, older patients are less likely to receive treatment than younger ones because of the concern for toxicity. An observational study of 675 patients who underwent colon resection for stage III CRC between 2003 and 2005 in five integrated healthcare delivery systems and 15 veterans hospitals in the USA [Kahn *et al.* 2010] found that from the 202 patients over 75 years old, only 101 (50%) received adjuvant chemotherapy and only 14% of those were given an oxaliplatin-containing regimen. Starting doses were lower than in the standard regimens tested in trials for 18% of patients. From the 101 patients, only 24 developed adverse events. Interestingly, older patients did not experience more adverse events than younger ones. This may be explained by the selection of less vulnerable patients and the lower starting doses administered. This may suggest that careful selection and adjusted doses for older patients may be appropriate, although such an approach has not been tested prospectively.

In another population-based analysis that compared the adverse outcomes between patients who received single agent 5FU or 5FU/oxaliplatin in the adjuvant setting [Sanoff *et al.* 2012a], there was modest evidence of increased toxicity from 5FU/oxaliplatin relative to 5FU with advancing age. Among patients aged at least 75 years, they observed a modest differential increase in adverse events from oxaliplatin but without increased need for emergency visits or hospitalizations.

Metastatic disease

The management of metastatic colorectal disease has been rapidly evolving in the last decade, with the increasing use of biological targeted agents and the development of advanced surgical and other related techniques. Twenty percent of patients of all age groups are diagnosed with synchronous liver metastasis and 33–50% of those are at least 70 years old [De Liguori Carino and Bonanni, 2013]. The possibility of liver or lung resection should always be considered during the initial evaluation of the patient, changing the therapeutic aim from palliative to curative. Older patients are often not offered liver metastasectomy. Only 6% of the total number of

patients who underwent liver resection were above 70 years old in 1990.This proportion gradually increased, reaching 25.8% in 2007 [Adam *et al.* 2010]. In a recent multicenter cohort study that evaluated the outcome of liver metastasectomy in patients over 70 years old, it was shown that older patients can achieve a reasonable 3-year survival rate, with an acceptable morbidity rate after liver resection. More specifically, 2-month postoperative mortality and morbidity rates were 3.8% and 32.3% compared with 1.6% and 28.7% of the younger patients respectively. Three-year overall survival was 57.1% for the older and 60.2% for the younger patients [Adam *et al.* 2010]. Patients considered unfit for general anaesthesia or major abdominal surgery are candidates for alternative ablative techniques, like radiofrequency ablation, microwave ablation or cryoablation. Although the survival rates yielded with these techniques are not comparable to those for liver resections, they may potentially improve the results of chemotherapy alone in selected cases. Data on the use of neoadjuvant treatment in older patients with unresectable disease are scarce. In a small comparative analysis of a single centre in Austria, 29 of 70 patients who were older than 70 years and underwent liver metastasectomy received neoadjuvant chemotherapy (with XELOX (capecitabine plus oxaliplatin) or 5FU). Patients who received XELOX had better response rates compared with those on 5FU (68% *versus* 0%) and better recurrence-free survival and OS compared with the others, with a safe administration profile [Tamandl *et al.* 2009].

For patients with unresectable disease and minor symptoms, a sequential treatment approach may be considered, aiming for the stabilization of disease and survival improvement. In this context, chemotherapy regimens may be changed before disease progression, 'maintenance' strategies can be used, and intervals 'off' treatment are given from time to time according to toxicity or patients' wishes. In this noncurative/palliative setting the risk of adverse events must be limited so they do not overshadow the survival and QOL potentially gained. The efficacy of 5FU is already proven and established in the treatment of metastatic disease compared with best supportive care. In a European population-based retrospective analysis in which 629 patients older than 70 years receiving 5FU for metastatic CRC were identified, it was shown that response rate and OS where similar between this age group and younger patients. Infusional 5FU was shown to be more effective than bolus 5FU in both age groups [Folprecht *et al.* 2004]. The safety profile of 5FU is comparable between older and younger patients, except for the incidence of severe mucositis, which is more likely in older patients (particularly with the bolus). Combination regimens, like FOLFOX, XELOX or FOLFIRI (Irinotecan plus infusional 5FU) (folinic acid, FU, irinotecan) are considered more effective than single-agent 5FU in patients with metastatic disease. Combined analysis of data taken from 2691 patients enrolled in phase III trials investigated whether older patients benefit to the same extent as younger ones from combination therapy with irinotecan in the first-line treatment of metastatic CRC [Folprecht *et al.* 2008]. Response rates were improved with irinotecan-based combination therapy compared with 5FU only in patients both younger than 70 years and older. Although the safety of this combination when administered as first line was confirmed in a phase III randomised trial that included 196 patients over 75 years old, a clear result of its superiority in terms of PFS was not proven [Mitry *et al.* 2012]. Later on, an ancillary study was performed to identify predictive factors of treatment feasibility and toxicity. Impaired Mini-Mental State Examination (MMSE) and Instrumental Activities of daily life assessment (IADL) were found to be predictive factors of grade 3–4 toxicity [Aparicio *et al.* 2013]. This indicates that cognitive function and dependency should be taken into account in the treatment choice of older patients.

MRC FOCUS 2, a UK randomized trial that was designed especially to target frail and older patients with advanced disease who would otherwise have been excluded from trials, included 43% patients above 75 years and 13% older than 80. After careful assessment, patients were randomized in four arms (infusional 5FU, 5FU plus oxaliplatin, capecitabine plus oxaliplatin and capecitabine single agent) with lower starting doses [Seymour *et al.* 2011]. In this study some benefit was suggested for the combination of 5FU plus oxaliplatin over the other treatments, although a superiority in terms of PFS was not met. Toxicity of grade 3–4 was not increased in this combination. One finding from this study with potential impact on clinical practice was that the use of capecitabine did not result in improvement in QOL compared with intravenous 5FU; on the contrary, it was associated with higher risk of grade 3 or worse toxicities.

Table 1. Studies regarding surgical approach for older patients diagnosed with early stage colorectal cancer.

Author/study	Type of study	No. of patients	No. of older patients (%)/ age cutoff (years)	Endpoints	Outcome
Damhuis *et al.* [1996]	Data analysis, retrospective	6457	1549 (24%)/ 80	(i) Resection rate (ii) 30-day postoperative mortality	(i) 82.1% for 80–89 years, 67.2% for >90 years (ii) 1.2% for <60 years, 9.8 % for >80 years
Rutten *et al.* [2008]	Data analysis (a) Dutch TME study (b) Dutch Comprehensive Cancer Centres	5923	1508 (25.4%)/ 75	Older *versus* younger patients: (i) 1 month (ii) 6-month postoperative (TME) mortality	(a) (i) 6.5% in patients aged 75–84 years *versus* 3.2% in patients aged 65–74 years (ii) 13.4% *versus* 4.6% (b) (i) 3.7% *versus* 1.1% (ii) 13.4% *versus* 4.9%
Aparicio *et al.* [2009]	Database analysis, retrospective	110	110 (100%)/ 75	Management analysis	52% received substandard treatment: 87% received surgical treatment 26% adjuvant CT 16% palliative CT
Fontani *et al.* [2011]	Observational analysis, prospective	914	352 (38.5%)/ 75	Older *versus* younger patients: (i) perioperative mortality (ii) 3-year, 5-year, 10-year OS	(i) 5.9% *versus* 2.1% ($p = 0.003$) (ii) 3-year OS: 37% *versus.* 52.3% 5-year OS: 16.2% *versus* 35.1% 10-year OS: 5.1 *versus* 24.7% ($p < 0.005$)
Maas *et al.* [2013]	Data analysis, retrospective	642 (a) $n = 346$ (b) $n = 296$	642 (100%)/ 75	Preoperative RT + surgery (a) *Versus* surgery alone (b): (i) local recurrence (ii) postoperative complications	(i) 2% *versus* 6% ($p = 0.002$) (ii) 58% *versus* 42% ($p < 0.0001$)

CT, chemotherapy; OS, overall survival; RT, radiation therapy; TME, total mesorectal excision.

Table 2. Studies regarding adjuvant treatment for older patients diagnosed with colorectal cancer.

Author/study	Type of study	No. of patients	No. of older patients (%)/ age cutoff (years)	Endpoints	Outcomes
Tournigand *et al*. [2012]	MOSAIQ subgroup analysis for stage II disease and older patients	2246	315 (14%)/ 70(<76)	FL *versus* FOLFOX4: (i) DFS (ii) OS	(i) HR 0.93 (95% CI 0.64–1.35, $p = 0.73$) (ii) HR 1.10 (95% CI 0.73–1.65, $p = 0.661$)
Sannof *et al*. [2012a]	Database analysis, retrospective, (SEER-Medicare, CanCONS, NCCN)	5489	5489 (100%)/ 75	OS in stage III: (i) CT versus no CT (ii) oxaliplatin-based treatment *versus* nonoxaliplatin regimens	(i) HR 0.60 (95% CI 0.53–0.68) (ii) SEER-Medicare: HR 0.84(95% CI 0.69–1.04) NYSCR-Medicare: HR 0.82 (95% CI 0.51–1.33)
McCleary *et al*. [2013]	ACCENT group analysis in stage II/III	14,528	2575 (21.5%)/ 70	FU *versus* combination regimens: DFS, OS,TTR in older (i) and younger (ii) patients	(i) DFS: HR: 1.05 (95% CI 0.94–1.19), $p = 0.09$ OS: HR 1.08 (95% CI, 0.95 to 1.23), $p = 0.05$ TTR: HR 1.06 (95% CI 0.93–1.22), $p = 0.36$ (ii) DFS: HR 0.89 (95% CI 0.80–0.99), $p = 0.001$ TTR: HR 0.88 (95% CI, 0.79–0.98), $p = 0.02$ OS: HR 1.08 (95% CI 0.95–1.23)*, $p = 0.04$

*The benefit of oxaliplatin addition is restricted to patients aged less than 70 years for OS. Oxaliplatin may benefit a subset of older patients in terms of DFS.
CI, confidence interval; CT, chemotherapy; fu, fluoropyrimidines; DFS, disease-free survival; HR, hazard ratio; OS, overall survival; TTR, time to recurrence.

Table 3. Chemotherapy studies for older patients with advanced/metastatic colorectal cancer.

Author/study	Type of study	No. of patients	No. of older patients (%)/ age cutoff (years)	Endpoints	Outcomes
Folprecht *et al.* [2008]	Pooled analysis (data from four phase III trials)	2691	599 (22.2%)/ 70	Iri/5FU *versus* 5FU as first line in younger *versus* older patients: (i) RR (ii) OS (iii) PFS	(i) RR: improved with Iri-based therapy Y:46.6 *versus* 29.0%, $p < 0.0001$ E: 50.5 *versus* 30.3%, $p < 0.0001$ (ii) OS: improved with combination therapy Y:HR 0.83 (95% CI 0.75–0.92; $p = 0.0003$) E: HR 0.87 (95% CI 0.72–1.05; $p = 0.15$) (iii) PFS improved with Iri-based therapy Y: HR 0.77 (95% CI 0.70–0.85, $p < 0.0001$) E: HR 0.75 (95% CI 0.61–0.90, $p = 0.0026$)
Cassidy *et al.* [2010]	Retrospective pooled analysis (AVF2107g, AVF219g, NO16966, E3200 trials)	3007	1142 (37.9%)/ 65	(i) PFS (ii) OS with FU-based CT ± Bev	(i) ≥ 65 years: 9.3 (+ Bev) *versus* 6.9 months HR 0.58 (95% CI 0.49–0.68, $p < 0.0001$) ≥70 years: 9.2 (+ Bev) *versus* 6.4 months HR 0.54 (95% CI 0.44-0.66, $p < 0.0001$) (ii) ≥65 years: 17.9 (+ Bev) *versus* 15 months HR 0.85(95% CI 0.74–0.97, $p = 0.015$) ≥70 years, 17.4 (+ Bev) *versus* 14.1 months HR 0.7 (95% CI 0.66–0.93, $p = 0.005$)
Adam *et al.* [2010]	Multicentre cohort study	7764	999 (12.8%)/ 70	Older *versus* younger patients with liver metastasectomy: (i) (a) postoperative mortality (b) morbidity (ii) OS (iii) DFS	(i) (a) 5 *versus* 2.2% for major hepatectomies ($p < 0.001$) 4.1 *versus* 0.9% for limited resections ($p < 0.001$) (b) 37.8 *versus* 35.2 % after major hepatectomy ($p = 0.19$) 30.3 *versus* 21.9% after limited resections ($p < 0.001$) (ii) 3 years: 57.1% *versus* 60.2% ($p < 0.001$) (iii) 3 years: 37% *versus* 31.9% ($p = 0.051$)
Seymour *et al.* [2011] (FOCUS2)	Multicentre, randomized phase III	438	199 (43%)/ 75	(a) Intravenous infusion 5FU (b) Ox + 5FU (c) Ox + Cap (d) Cap (i) PFS: (a) *versus* (b), (c) *versus* (d) (ii) QOL assessment with Cap instead of 5FU	(i) 5.8 *versus* 4.5 months, HR 0.84 (95% CI 0.69–1.01, $p = 0.07$) (ii) Replacement of FU with Cap did not improve QOL
Cunningham *et al.* [2013] (AVEX)	Multicentre, randomized phase III	280	280 (100%)/ 70	(i) PFS (a) Cap ($n = 140$) (b) Cap + Bev ($n = 140$) (ii) assessment of treatment-related AE	(i) 9.1 (+ Bev) *versus* 5.1 months HR 0.53 (95% CI 0.41–0.61, $p < 0.0001$) (ii) ≥Grade 3: 40% (+ Bev) *versus* 22% serious AEs in 14% and 8% respectively

5FU, 5 fluorouracil; AE: adverse event; Bev, bevacizumab; Cap, capecitabine; CI, confidence interval; CT, chemotherapy; DFS, disease-free survival; E, elderly group; HR, hazard ratio; Iri, irinotecan; OS, overall survival; Ox, oxaliplatin; PFS, progression-free survival; QOL, quality of life; RR, response rate; Y, younger group.

Targeted therapies

Up until a few years ago, clinicians were reluctant to use targeted therapies in older patients with metastatic CRC as data available for their efficacy and toxicity were limited. Additionally, the higher cost of these agents in combination with the lower life expectancy of older patients made the decision for their use even more difficult.

Recently, data from the 'AVEX' trial, a multicenter phase III randomized trial investigating the efficacy and safety of adding bevacizumab to single-agent capecitabine in an older patient population, showed that PFS was significantly longer in the group of patients who received bevacizumab plus capecitabine *versus* the capecitabine alone group (9.1 *versus* 5.1 months, $p < 0.0001$). All 280 patients recruited were over 70 years old and interestingly these were patients previously not deemed fit for oxaliplatin or irinotecan-based chemotherapy. Also, more patients in the combination group achieved a response compared with those receiving capecitabine monotherapy (19% *versus* 10%, $p = 0.04$). The OS did not differ significantly between the two groups. The frequency of bevacizumab-related side effects, such as haemorrhage, hypertension, arterial/venous thromboebolic events and proteinuria, was higher in the combination group as expected. However, the frequency of grade 3 or worse adverse events, of all kinds, were more or less similar in the two groups, with the exception of hand–foot syndrome and the arterial thromboembolic events. In general, the combination of capecitabine plus bevacizumab proved to be a safe therapeutic option for this group of patients [Cunningham *et al.* 2013].

The findings of the AVEX trial are consistent with previous conclusions from an analysis of four randomized trials, published in 2010, by Cassidy and colleagues [Cassidy *et al.* 2010]. Three of those referred to first-line treatment and one to second-line treatment. Patients were treated with fluoropyrimidine-based chemotherapy with or without bevacizumab. Addition of bevacizumab to chemotherapy significantly prolonged PFS in older and younger patients. Again, toxicity rates were generally similar in older and younger patients, except for thromboembolic events, which were more common in the older group. The same encouraging findings came out of a subgroup analysis of the AGITG MAX trial. In 99 patients aged 75–86, addition of bevacizumab to capecitabine resulted in improved PFS (8.8 *versus* 5.8 months), with no significant trends to greater toxicity effects by age, apart from a greater rate of diarrhoea with the addition of bevacizumab [Price *et al.* 2012].

The concern about arterial thrombotic events (ATEs) with the use of bevacizumab may be somewhat overestimated. As it was shown by a recent population-based cohort study among patients aged over 65, the risk is similar to the results from randomized clinical trials that mostly included younger populations. Although a statistically significant increased hazard ratio of ATEs was found, when this difference was expressed in absolute terms it accounted only for four additional ATE cases per 1000 person-years. This information could have a clinical impact on the decision making of the physician and the patient who may be willing to accept the risk for the survival prolongation benefit [Tsai *et al.* 2013].

Treatment with cetuximab is less studied in older patients and the evidence is less clear compared with bevacizumab. However, it seems to be an alternative choice for older patients with kras wild type disease. As shown by the Spanish TTD group study that delivered a subgroup analysis based on the kras status, cetuximab in combination with capecitabine is a safe and efficient treatment option in older patients with advanced wild-type kras CRC with a response rate of 48.3% compared with 20.7% of those with Kras-mutant status [Sastre *et al.* 2012]. One German noninterventional observational study evaluated the efficacy and safety of cetuximab in combination with chemotherapy in 614 pretreated patients with metastatic CRC and reduced performance status who were aged 18–65 and over 65 years. Cetuximab was administered in combination with chemotherapy in different doses (8% received cetuximab alone). Although Kras status was not taken into account in this study, the response rate reached up to 37% with a PFS of 6.9 months. The commonest toxicity was skin rash in all ages. The prevalence of skin rash was similar between both age groups, however the older group showed a trend towards higher grades and duration of toxicity. All other toxicities (gastrointestinal, hepatic, haematologic toxicities and infusion reactions) had a similar prevalence between age groups. Unfortunately the follow-up period in this study was limited to 12 months. Still, it indicated that older patients with reduced performance status and comorbidities can be treated effectively and safely with cetuximab as

second- or third-line treatment [Jehn *et al.* 2012]. In a pooled analysis of the CRYSTAL and OPUS trials, which tested the efficacy of cetuximab in combination with FOLFIRI and FOLFOX respectively, according to kras status, cetuximab provided PFS and OS benefit in older patients who were treated with the combination compared with chemotherapy alone: 8.9 *versus* 7.2 months for PFS and 23.3 *versus* 15.1 months for OS [Folprecht *et al.* 2010].

Toxicity and individualization

As the procedure of aging is accompanied by vital organ function decline, special care should be taken with dosing in older patients as they may have altered drug metabolism and elimination. More specifically, dose reductions are required in cases of renal impairment when capecitabine is administered.

Lower bone marrow reserves make older patients more susceptible to severe and prolonged cytopenia, for which dose reductions, schedule delay or haemopoietic growth factor support may be considered.

Treating older patients with CRC can be very challenging due to their heterogeneity. Multiple factors must be taken into consideration when assessing an older patient. Apart from their performance status, which is commonly used in oncologic assessment, the comorbidities, basic organ function, possible cognitive impairment, nutritional status and socioeconomic background affecting their daily life habits must be thoroughly assessed. Frailty and malnutrition have been correlated with increased mortality risk in patients receiving palliative chemotherapy [Aaldriks *et al.* 2013]. Thus, the use of geriatric assessment tools must be ideally implemented in daily practice. Generalizing and decision making based solely on age categorization should be abandoned. Personalization of decisions is key in the care of older patients and multidisciplinary teams should develop a primary role in this.

Assessment should begin preoperatively. PACE (Preoperative Assessment of Cancer in the Elderly) is a valuable tool in enhancing the decision-making process of whether a patient is a suitable candidate for surgical intervention. It has been observed that a large number of patients are considered unfit only because of their biological age in combination with inaccurate risk assessment. PACE includes a number of instruments, such as the MMSE, activities of daily living (ADL), IADL, Geriatric Depression Scale, Brief Fatigue Inventory (BFI), Eastern Cooperative Oncology Group performance status, American Society of Anaesthisiologists Scale and Satariono's Index of Comorbidity. The likelihood of having a postsurgical complication is increased by approximately 50% when patients have a high IADL score, abnormal performance status score or a moderate/severe BFI measured prior to surgery. This has been concluded from a multicenter prospective study from five countries between July 2003 and December 2005 [Audisio *et al.* 2008]. In the same study no relationship between comorbidities and postsurgical outcomes was observed. Even though no randomized controlled trial has examined the effectiveness of geriatric assessment in the oncology setting, distinguishing between fit and frail vulnerable patients, irrespective of their age, treatment goals can be maximized or compromised to best supportive care, avoiding complications. The Comprehensive Geriatric Assessment tool delivered in various forms, like self assessment or during clinical interview, can be valuable following referral from the surgeon. Apart from the toxicity concerns, the personal wishes of older patients should not be ignored in the decision on further treatment. This applies to the initiation of treatment as well as to the wish for treatment interruption. Although, older patients prefer less information and less involvement than younger patients, in a recent study among patients with CRC, 60% of the older group wanted detailed information about chemotherapy and 83% wanted involvement in decision making [Jorgensen *et al.* 2013]. The factors influencing their decisions were fear of dying, their health status, age, QOL and understanding the treatment and its side effects. Constant reevaluation and reassessment throughout every step of treatment, not only prior to initiation, is crucial. Continuous and close monitoring for early detection of side effects is essential.

Summary

Although CRC is a disease of aging, older patients are under represented in clinical trials, often understaged and undertreated. The stereotypes that consider the chronological age as a factor of unfitness for treatment should be abandoned. A multidisciplinary approach and an overall treatment plan should be established soon after the diagnosis and proper staging, taking into account the patient's personal wishes.

Surgery which is the cornerstone of treatment should not be abandoned lightly, as operative outcomes are not considered to be worse in older patients compared with younger patients. Emergency surgery should be avoided when possible and a two-stage procedure or the use of stents should be considered. The less traumatic procedures, like laparoscopic operations, are preferred when feasible. Age should not be a criterion for exclusion of patients from metastasectomies. All patients should be managed in the context of a multidisciplinary team.

Chemotherapy use, both in the adjuvant and palliative setting, should be offered to older patients and their management should not differ substantially from that of younger patients. Combination treatments and targeted therapies are not prohibitive but should be used with critical clinical judgment, with constant and careful monitoring for early detection and treatment of toxicities, along with best supportive care.

In conclusion, as in every aspect of medical care, all therapeutic decisions for older patients with CRC must be made on an individual basis. Finally, prospective studies specific to the older population are needed so that clear, contemporary evidence-based guidelines can be developed.

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Conflict of interest statement

The authors declare no competing interests.

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