Treatment of the elderly colorectal cancer patient: SIOG expert recommendations


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Colorectal cancer (CRC) is one of the commonest malignancies of Western countries, with approximately half the incidence occurring in patients >70 years of age. Elderly CRC patients, however, are understaged, undertreated and underrepresented in clinical trials. The International Society of Geriatric Oncology created a task force with a view to assessing the potential for developing guidelines for the treatment of elderly (geriatric) CRC patients. A review of the evidence presented by the task force members confirmed the paucity of clinical trial data in elderly people and the lack of evidence-based guidelines. However, recommendations have been proposed on the basis of the available data and on the emerging evidence that treatment outcomes for fit, elderly CRC patients can be similar to those of younger patients. It is hoped that these will pave the way for formal treatment guidelines based upon solid scientific evidence in the future.

Key words: chemotherapy, colorectal cancer, elderly, geriatric, radiotherapy, surgical management

introduction

The fastest growing section of the population in Western countries is that of people over the age of 65 years. This means that more people are living long enough to develop cancer. The consequences of this are not only an anticipated increase in the overall cancer incidence but also in the number of elderly cancer patients wanting and requiring treatment. In Europe and the United States, >60% of new cancer cases and >70% of cancer deaths occur in those aged 65 years or older [1]. Approximately 50% of colorectal cancer (CRC) patients are >70 years of age and in this age group CRC is the second most common cause of cancer death [2]. However, the relative survival of elderly (≥65 years) CRC patients is generally worse than that of younger patients due to more advanced stage at presentation and also due to the fact that they often receive suboptimal management [3–5]. The question is ‘what constitutes an elderly patient?’ Not only can chronological age be very different from biological age but also the definition of ‘elderly’ differs from anything between 265 years and ≥80 years for different trials.

The majority of patients with stage I or II CRC are cured by surgery alone, although a small percentage of patients with stage II disease may derive additional benefit from adjuvant therapy [6, 7]. The standard treatment of stage III colon cancer is surgery followed by adjuvant chemotherapy, while in patients with metastases systemic chemotherapy either alone or in combination with newer targeted agents is usually the treatment of choice, with surgical intervention where appropriate. In patients with synchronous metastases, the best sequence of therapy in most patients is probably resection of the primary (if at all), followed by chemotherapy and resection of metastases if appropriate, but this is still under debate. The important thing is that a multidisciplinary team defines the general treatment strategy from the outset. If the treatment is to be administered with palliative intent, to prolong survival and improve quality of life, the least toxic but most active chemotherapy option should be chosen. On the other hand, if the intent is curative, e.g. the administration of neoadjuvant chemotherapy to facilitate the secondary resection of potentially resectable hepatic metastases, higher levels of toxicity may be deemed acceptable in order to achieve this goal and thus a more toxic chemotherapy regimen recommended. The situation is similar for the treatment of stages III and IV rectal cancer, which involves surgical resection and preoperative or postoperative, radiation therapy and/or chemotherapy (www.cancer.gov/cancer topics). However, in Europe, treatment strategies for rectal cancer for the most part can be divided into preoperative treatment with radiotherapy...
alone (short course) or a combination of chemotherapy and radiotherapy (long course).

Evidence from population-based studies clearly demonstrates that older patients are more often inadequately staged, undergo fewer elective operations [8] and are less likely to receive adjuvant chemotherapy and/or radiotherapy than their younger counterparts [4, 9–12]. Surgery in particular may be withheld due to concerns about postoperative morbidity and mortality [13]. However, it could be argued that as elderly individuals are underrepresented in clinical trials, the data for the inclusion of surgery, radiotherapy or chemotherapy alone or in combination in the treatment plan are weaker [1, 14].

A population-based study of 5874 patients, from the Burgundy Cancer Registry, showed survival trends to have improved over time but to differ markedly according to age [15]. In elderly people, the improvement in overall survival (OS) could be attributed to an increase in the proportion of patients undergoing resection on a curative basis. In the younger (<75 years) patients, there was also an increase in the rate of potentially curative resections but additionally there was a significant, stage-specific improvement in survival for stage III patients presumably due to adjuvant chemotherapy [15]. In another study, using the Burgundy Cancer Registry, only 34% of patients ≥75 years were resected with curative intent compared with 53% of younger patients (P = 0.001) [16]. Survival rates, not surprisingly, were higher for the younger patients (<75 years) than they were for the older patients, and survival improved over time for those with both distant metastases and local recurrence (P < 0.0001) [16].

The reasons why elderly patients are less likely to be offered ‘optimal treatment’ include the fact that they are less likely to be referred to specialists with the appropriate knowledge to make the decision, often due to concerns over their physical and mental frailty, and the fact that they are more likely to have comorbidities and age-specific deteriorating organ function, which could make their tolerance of surgery and/or chemotherapy in particular more difficult to manage. These perceptions continue despite emerging evidence that fit, elderly, CRC patients seem to have a relative survival that is very similar to that of their younger counterparts when given comparable treatment. It was against this backdrop that International Society of Geriatric Oncology (SIOG) established a task force to review the available evidence and arrive at appropriate recommendations.

methods

The task force comprised one geriatric medicine specialist, one surgeon, two radiation oncologists and five medical oncologists. The key areas for discussion were structured under five headings.

key areas for discussion

1. Diagnosis, staging and patient assessment
2. Surgical management of the elderly patient
3. Radiotherapy in rectal cancer in the elderly patient
4. Chemotherapy and targeted therapies in the elderly CRC patient
5. Palliative versus curative therapy in the elderly

Each area overview was presented by one of the task force experts and comments invited from the other task force members.

results

diagnosis and assessment in geriatric patients

A clear goal was to establish what was required for diagnosis and what was required in terms of patient assessment. The peak incidence for CRC is between 70 and 80 years of age suggesting that the elderly population is the right target for screening and diagnosis. However, it needs to be remembered that as screening is targeted at precancerous adenomas with a 5- to 10-year lead time for the development of carcinoma, screening needs to be carried out in patients between 60 and 70 years of age. To this end the benefits and shortcomings of a range of screening, diagnostic and preoperative assessment techniques such as the fecal occult blood test (FOBT) [17–22], barium enema [23, 24] sigmoidoscopy [25, 26], colonoscopy [27–29], computed tomography (CT) colonoscopy/colonography for diagnosis [30, 31] and for screening [32–34] ultrasound scan [35], CT scan or magnetic resonance imaging (MRI) scan [36] and a variety of assessment scales [37] were reviewed and discussed. Cost effectiveness was also considered [38–40], as well as the influence of socioeconomic status [41].

Although the data refer almost exclusively to screening in nonelderly populations, and despite the earlier statement that screening of patients needs to commence ~10 years ahead of peak incidence, elderly individuals also need to be screened. After all, not only are individuals between 70 and 80 years of age at the highest risk of developing CRC but also the median life expectancy of an 80-year-old today is estimated to be a further 11 years for women and a further 9 years for men, of which 9 and 7 years, respectively, are enjoyed without disabilities. In addition, screening using the FOBT has also been seen to reduce the number of emergency presentations of CRC [22], and the incidence of emergency presentations is higher in elderly patients. Finally, elderly individuals need to be screened so that, at the very least, they are not excluded from palliative care.

Furthermore, it is important not only to the patient but also to the health-care providers that only those elderly patients who will benefit from therapy are treated [37, 42]. Thus, those elderly patients where a diagnosis of CRC will not change their already frail state, and for whom no benefit can be achieved, should not be subjected to potentially harmful therapy.

recommendations for screening, staging and diagnosis. The SIOG recommendations for screening are that FOBT should be encouraged at a national level through well-designed screening programs, with colonoscopy and sigmoidoscopy as and when appropriate, and careful thought given to the target age groups. It needs to be remembered that as the age of those screened increases, the potential for complications increase, particularly in relation to colonoscopy.
The recommendations for diagnosis of tumors of the colon or rectum were as follows:

- Suspected cancer of the colon and rectum should be confirmed by colonoscopy.
- For confirmed cancer of the colon, a CT of the chest and abdomen and an MRI or ultrasound scan of the abdomen plus chest x-ray (CXR) should be undertaken for staging.
- For confirmed rectal cancer, an MRI scan of the pelvis and a CT of the chest and abdomen. MRI or ultrasound scan of the abdomen plus CXR should be undertaken.
- Patients should be followed up with routine colonoscopy and/or sigmoidoscopy depending on the site of the primary tumor and according to local practice.

In terms of assessment, it was recommended that due to the heterogeneity of the elderly patient population, patients >65 years of age needed to undergo a preoperative evaluation, which should include a cancer-specific assessment as well as a whole patient evaluation for the most common physiological side-effects of aging, physical and mental ability and social support. In the case of a patient with physical or psychological comorbidities as measured by the comprehensive geriatric assessment (CGA) [37, 43], or by local screening methodology, a geriatrician should be involved in patient management.

There are, however, many limitations to these recommendations. Firstly, as stated previously, there is the issue of the frequent discrepancy between chronological age and biological age, with the additional complication that many elderly patients have coexisting medical, potential psychological biological age, with the additional complication that many elderly patients have coexisting medical, potential psychological side-effects of aging, physical and mental ability and social support. In the case of a patient with physical or psychological comorbidities as measured by the comprehensive geriatric assessment (CGA) [37, 43], or by local screening methodology, a geriatrician should be involved in patient management.

There are, however, many limitations to these recommendations. Firstly, as stated previously, there is the issue of the frequent discrepancy between chronological age and biological age, with the additional complication that many elderly patients have coexisting medical, potential psychological and social care issues. Secondly, there is an amazing paucity of data about CRC in patients >75 years of age.

**Surgical management of the elderly patient**

Surgery is indisputably the most successful treatment modality for colorectal tumors. The improvement in the survival of CRC patients over time has mostly been due to a decrease in operative mortality and an increase in the resection rate, possibly coupled with a more aggressive approach to the treatment of local or distant recurrences [15, 16, 44, 45].

A registry-based study of 6457 patients with CRC, diagnosed between 1985 and 1992 in hospitals connected to the Rotterdam Cancer Registry, emphasizes the disparity in the treatment patterns between elderly and younger patients [13]. Overall, 87% of the patients underwent resection, but the resection rates were lower for patients >89 years (67%) and for patients with rectal cancer (83%). The postoperative mortality rate was 1% for patients <60 years of age and steadily increased with age. For patients >80 years of age, the operative risk was 10%. According to multivariate analysis gender, age, subsite and stage were defined as independent prognostic factors [13]. Another study in patients in their eighth and ninth decades showed postoperative mortality to increase from 8% between 80 and 84 years to 13% between 85 and 89 years and to 20% for those in their 90s [46].

A systematic review of the published and aggregated data, from 28 independent studies and 34194 patients, conducted by the Colorectal Cancer Collaborative Group [8] compared the outcomes for patients aged 65–74 years, 75–84 years and 85+ years with those for patients aged <65 years. The findings showed that elderly patients had an increased number of comorbidities, were more likely to present with later-stage disease, were more likely to undergo emergency surgery and again were less likely to have curative surgery than younger patients. As for the Rotterdam study, the incidence of postoperative morbidity and mortality increased progressively with advancing age. OS was also reduced in elderly patients, but for cancer-specific survival, the age-related differences were much less striking. Thus, the relationship between age and outcomes from CRC surgery is complex and may be confounded by differences in stage at presentation, tumor site, preexisting comorbidities and the type of treatment received. However, there is little doubt that carefully selected, even very old patients benefit from surgery, since a large proportion survive for 2 or more years postsurgery, irrespective of their age. In support of this, the recommendation from an analysis in 9301 rectal cancer patients >80 years of the long-term outcome after surgical intervention states, ‘age should not deter surgeons from offering optimal therapy to good-risk patients’ [47].

In a separate study, age was shown not to be a factor for local recurrence with the rate of distant recurrence being less in the elderly group [48]. While in another study, preexisting comorbidities strongly influenced the type of resection (elective versus emergency) and as a consequence long-term outcome [49]. In the case of elective surgery, long-term cancer-related and short-term morbidity and mortality outcomes for elderly patients are similar to those in younger patients [50]. Furthermore, there is clear evidence that CRC patients ≥70 years, undergoing liver resection, achieve clinically significant progression-free [51, 52] and 5-year survivals (Table 1) [51]. This is important in light of the recommendation that liver resection should be undertaken in patients with hepatic metastases wherever possible [53]. Mortality is, however, higher in those over the age of 70 (4.5% versus 1.5%) [54].

The use of Preoperative Assessment of Cancer in the Elderly (PACE), which is a composite of validated questionnaires, including the CGA and others such as the Eastern Cooperative Oncology Group performance status, American Society of Anesthesiologists questionnaire, Physiological and Operative Severity Score for enUmeration of Mortality and Morbidity (POSSUM) and the Portsmouth variation of POSSUM plus pathological data, has identified the factors that impinge on outcome [55–58]. The results of a pilot study showed the PACE questionnaire, which took ~20 min to complete, to be practical.

**Table 1. Curative resection for colorectal cancer liver metastases in elderly patients** [51]

<table>
<thead>
<tr>
<th>Age group</th>
<th>&lt;70 years</th>
<th>≥70 years</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>144</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>Morbidity</td>
<td>20.7%</td>
<td>14.6%</td>
<td>0.18</td>
</tr>
<tr>
<td>Mortality</td>
<td>5.7%</td>
<td>2.1%</td>
<td>0.19</td>
</tr>
<tr>
<td>Five-year survival</td>
<td>38%</td>
<td>30%</td>
<td>NS</td>
</tr>
<tr>
<td>Disease-free survival</td>
<td>25 months</td>
<td>23 months</td>
<td>NS</td>
</tr>
</tbody>
</table>
and inexpensive and to be clearly comprehended by, and acceptable to, patients. It also served to identify PACE items associated with general morbidity (Table 2) and those specifically associated with 30-day postoperative morbidity (Table 3) [59, 60].

Thus again, the available evidence suggests that long-term survival for fit, elderly CRC patients undergoing surgery is similar to that of younger patients, although it is recognized that OS is poorer in elderly patients due to other factors. The recommendations for cancer surgery for elderly patients with CRC are listed below.

**recommendations.** The general consensus was that:

- Emergency colorectal surgery, due to foreseeable complications, should be avoided wherever possible.
- The use of colorectal stents should be considered whenever appropriate to improve patient nutrition with a view to facilitating elective surgery 1–2 weeks after the patient has presented as an emergency.
- Elective surgery with a prospective analysis of the perioperative variables and careful treatment planning should be the pathway of choice.

**Table 2.** Association of PACE items with morbidity (SIOG Proceedings, The Hague, 2–4 November 2006)

<table>
<thead>
<tr>
<th>PACE item</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>2.92</td>
<td>1.49–5.74</td>
<td><strong>0.002</strong></td>
</tr>
<tr>
<td>Mini-Mental State</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No deficit</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficit</td>
<td>1.53</td>
<td>0.92–2.54</td>
<td>0.140</td>
</tr>
<tr>
<td>Activities of daily living</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>1.91</td>
<td>1.09–3.34</td>
<td><strong>0.024</strong></td>
</tr>
<tr>
<td>Instrumental activities of daily living</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Independent</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dependent</td>
<td>2.12</td>
<td>1.38–3.25</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>Geriatric Depression Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No depression</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depressed</td>
<td>1.82</td>
<td>0.98–3.38</td>
<td>0.057</td>
</tr>
<tr>
<td>Brief Fatigue Inventory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No fatigue</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigued</td>
<td>2.27</td>
<td>1.39–3.71</td>
<td><strong>0.001</strong></td>
</tr>
<tr>
<td>American Society Anaethesiologists Grading</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.15</td>
<td>0.65–2.03</td>
<td>0.636</td>
</tr>
<tr>
<td>2–4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.99</td>
<td>0.45–1.98</td>
<td>0.984</td>
</tr>
<tr>
<td>1</td>
<td>1.74</td>
<td>0.86–3.52</td>
<td>0.121</td>
</tr>
<tr>
<td>3+</td>
<td>1.89</td>
<td>0.98–3.64</td>
<td>0.058</td>
</tr>
</tbody>
</table>

PACE, Preoperative Assessment of Cancer in the Elderly; SIOG, International Society of Geriatric Oncology.
The numbers in bold denote statistical significance.

- Healthy, elderly patients should not be excluded from potentially curative resection of their hepatic metastases provided they undergo careful preoperative assessment and receive good postoperative care.

**radiotherapy in the treatment of rectal cancer in the elderly in the adjuvant and palliative settings**

Approximately a third of CRC patients present with rectal cancer. Extraction of the data for 838 rectal cancer patients >80 years from the Cote d’Or and Calvados tumor registries study [44] showed a marked improvement in 5-year survival rates over a period of two decades from 18% in 1978–1981 to 41.7% for the period 1994–1997 (J-CH, personal communication). This was attributed to earlier diagnosis and an increase in the number of patients who were managed with curative intent, mostly surgical, with a marked reduction in perioperative mortality. More recently, the use of the surgical technique total mesorectal excision (TME) [61] has lead to a marked reduction in pelvic recurrences. However, analysis of 991 treatments, in the 838 elderly rectal cancer patients from these registries, showed 54% of patients to undergo curative resection, 7% to undergo palliative resection, 12% to undergo by-pass laparotomy, 27% to undergo no surgery, 17% to receive radiotherapy and 2% to receive chemotherapy. These data clearly demonstrated the insufficient use of radiotherapy either combined with surgery or alone, while chemotherapy was almost never administered. A more detailed analysis per stage shows that ~50% of these patients should have been considered eligible for pre- or postoperative radiotherapy.

These shortcomings in our approach to the care of the elderly, rectal cancer patient are confirmed by an unpublished report based on the data from 12 cancer registries on the management of rectal cancer in France in 2000 (Anne Marie Bouver, Guy Lanois, Jean Faivre et le réseau FRANCIM, unpublished data). Overall, 84.7% of primary rectal tumors were resected but the resection rates were 89.7% for patients...
The study clearly highlighted significant variations in patient management despite access to Good Clinical Practice Guidelines and consensus statements, with insufficient access of patients to radiotherapy and research trials (0.8% compared with 7.7% in the younger age group). The variations in relation to radiotherapy were of particular significance because radiotherapy can facilitate R0 resection in initially unresectable cases, prevent local recurrences after good R0 resection and can palliate symptoms such as pain and bleeding. Radiotherapy has also been shown to impact significantly on survival in resectable tumors [62] and is also important for the management of patients with all stages of rectal tumors, from superficial T1 in patients with a 90% cure rate with contact X-ray therapy [63], to advanced inoperable T4 tumors treated with radiotherapy, combined or not with contact X-ray and/or interstitial brachytherapy. The influence of radiotherapy on the treatment of rectal cancer is one of the best-evidence-based treatments in oncology. However, there are very few patients in radiotherapy trials who are aged >75 years [62, 64–68].

Over the years, the use of radiation coupled with improved surgical technique has lead to a reduction in the local recurrence rate and long-term prevention of recurrence [62, 64]. All the trials involving short-term preoperative radiotherapy, including the Dutch randomized trial in which patients underwent standardized TME resections, showed lower local recurrence rates in the radiotherapy arms [66], and one can assume that it is probably the same in an elderly cohort. Certainly, the evidence suggests that the survival gains from preoperative radiotherapy are the same irrespective of age [8] but that tolerability is not. Data from the Colorectal Collaborative Group [8] clearly indicate that the number of deaths from rectal cancer is reduced as a consequence of preoperative but not postoperative radiotherapy, although the census data for this exclude data from the last 6 years. The analysis also showed there to be an increased number of deaths from other causes within the first year after preoperative radiotherapy and slightly for postoperative radiotherapy particularly in the elderly group. Acute tolerability to radiotherapy is dose- and volume dependent, and older people are more susceptible than younger patients [69]. Analysis of the data from the Stockholm I trial showed the postoperative mortality to be increased in patients >75 years (Table 4) [69, 70]. However, it was clearly related to a large pelvic and mesenteric target and treated volume. The reduction of the target volume, to the posterior pelvis only, in the Stockholm II trial was sufficient to eliminate such risk and probably contributed to the demonstration of a survival benefit in addition to the reduction in pelvic recurrences [62].

### Table 4.

<table>
<thead>
<tr>
<th>Preoperative radiotherapy (n = 424)</th>
<th>0 radiotherapy (n = 425)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;75 years, 75+</td>
<td>&lt;75 years, 75+</td>
</tr>
<tr>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>16%</td>
<td>8%</td>
</tr>
<tr>
<td>8%</td>
<td>2%</td>
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<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Table 5. Noncancer-related mortality and radiotherapy surgery interval (Marijen, thesis)

<table>
<thead>
<tr>
<th>In-hospital mortality</th>
<th>Noncancer deaths at 24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>TME</td>
<td>3.3%</td>
</tr>
<tr>
<td>TME + RT: all</td>
<td>4.0%</td>
</tr>
<tr>
<td>TME + RT &lt;3 days</td>
<td>2.5%</td>
</tr>
<tr>
<td>TME + RT 3+ days</td>
<td>5.6%</td>
</tr>
<tr>
<td>TME + RT &lt;3 days, 75+</td>
<td>5.6%</td>
</tr>
<tr>
<td>TME + RT 3+ days, 75+</td>
<td>5.6%</td>
</tr>
</tbody>
</table>

TME, total mesorectal excision; RT, radiotherapy.
• TME with adequate quality assurance and quality control of the procedure
• Preoperative radiotherapy where appropriate using $5 \times 5$ Gy and immediate surgery (2–3 days) or 40–50 Gy protracted radiotherapy over 4–5 weeks. In both cases, it is essential to reduce the target volume to the posterior pelvis and to use modern treatment planning based upon three-dimensional imaging reconstructions.
• Preoperative long-course RTCT may be more effective than long-course RT alone, but we do not know this for those >75 years and will probably not be tolerated by the very elderly group.
• In locally inextirpable tumors (T4 with overgrowth to tissues that are not easy to resect), prolonged RTCT is the treatment of choice, in elderly patients fit enough for this therapy. A $5 \times 5$ Gy with a long delay of 6–8 weeks is a new option in the very old [75, 77].
• Radiotherapy should be used to manage inoperable patients with low rectal tumors (all stages) and similarly in the palliative advanced disease setting.

topic

chemotherapy in the treatment of CRC in the elderly

Chemotherapy is used in the adjuvant setting for the treatment of stage III and high-risk stage II disease and also in the treatment of advanced, usually metastatic, disease.

adjuvant. The use of adjuvant chemotherapy is intended to eradicate any residual micrometastatic disease following potentially curative surgical resection. However, the use of such treatment in patients >70 years of age remains controversial due to concerns over both toxicity and death due to causes other than cancer.

A pooled analysis of 3351 patients with stage II/III colon cancer from seven studies, treated with 5-fluorouracil (5-FU) plus folinic acid (FA) (five trials) or levasimole (two trials), showed adjuvant treatment to have a statistically significant positive effect on both OS and time to recurrence ($P < 0.001$ with hazard ratios (HRs) for death and recurrence of 0.76 and 0.68, respectively), when compared with surgery alone [78]. Furthermore, no significant interaction was observed between age and efficacy of treatment, and the incidence of toxicity was not increased in patients >70 years except for leucopenia in one study. However, analysis of the four different age groups ($\leq$50 years, 51–60 years, 61–70 years and >70 years) showed the probability of death without recurrence of cancer to be strongly associated with age. Patients 50 years old or younger had a 2% chance of death unrelated to cancer while those >70 years had a 13% chance [78]. A population-based study, of 4768 stage III colon cancer patients $\geq$65 years, between 1992 and 1996, in which half the patients received adjuvant therapy, showed 5-FU-based adjuvant therapy to be significantly associated with reduced mortality [HR for death was 0.66 (95% confidence interval 0.60–0.73)] [12]. Another retrospective review of 85 934 patients with stage III colon cancer, between 1990 and 2002, showed the use of adjuvant chemotherapy to be lower in the elderly being 80%, 70% and 40% in patients of <70 years, 70–79 years and >80 years, respectively [79]. However, adjuvant chemotherapy was shown to increase survival in the elderly in the same way as in younger patients.

More recently, the randomized X-ACT trial of adjuvant capcitabine versus bolus 5-FU/FA in patients with stage III colon cancer, and an upper age limit of 75 years (although patients up to 82 years were included), showed there to be no difference in terms of safety, for those patients <65 years and those $\geq$65 years [80]. However, it should be pointed out that specific guidelines for renal impairment should be applied when using capcitabine [81]. Nevertheless, in a recent 5-year efficacy update from this trial presented at this year’s American Society of Clinical Oncology Gastrointestinal Cancers Symposium, age was shown to be a significant factor on a multivariate analysis for OS [82]. UFT (oral uracil with tegafur plus FA) has also been shown to be equally effective with comparable toxicity when compared with bolus 5-FU/FA in patients <60 and $\geq$60 years [83]. A retrospective review, from the Royal Marsden Hospital, of the use of adjuvant and palliative chemotherapy for the treatment of CRC in 310 patients 70 years or older showed the elderly patients to experience mucositis with the bolus regimen but no other differences in toxicity [84]. In the MOSAIC study of adjuvant FOLFOX4 versus infusional 5-FU/FA, both younger and older patients (≥70 years of age but ≤75 years) received benefit from FOLFOX4 [85]. Nevertheless, when considering the above study, certain limitations need to be taken into consideration, including an eligibility of up to 75 years and the fact that these were patients deemed fit for entry into a clinical trial. In addition, it should be noted that no population-based studies with this combination regimen are as yet available and there is no information for patients $\geq$75 years.

Thus, toxicity may not be a major issue for the fit, elderly colon cancer patient. Administering adjuvant chemotherapy for at least 5 months on the other hand may be important in terms of efficacy, as demonstrated by a study in colon cancer patients who were >65 years of age [9].

As stated previously, the survival gain, in older patient populations, is difficult to assess due to an increase in deaths from other causes. In a recent publication on the use of adjuvant chemotherapy mostly in patients with stage II disease from the QUASAR Collaborative Group, it was argued that by age 80, adjuvant chemotherapy can only show a very small net benefit even with the highest estimate for treatment efficacy [86]. The multiple regimens available to consider also make the decision-making process more difficult. Therefore, it is difficult to recommend adjuvant therapy for all elderly patients.

Although adjuvant therapy trials have included very few patients $\geq$80 years, the evidence for the elderly patient’s ability to tolerate chemotherapy in general (see below) suggests that age alone should not exclude any stage III colon cancer patient from consideration for adjuvant therapy. On the other hand, there are very little data for over 75s and at this point for this age group, age alone may be a legitimate consideration. The recommendations for the ongoing adjuvant treatment of the elderly are outlined below.
recommendations. For the adjuvant treatment of elderly patients with stage III CRC, the chemotherapy regimens that can be considered are as follows:

- Infusional 5-FU
- Bolus 5-FU modulated by leucovorin (however, because of the potential increase in toxicity associated with the use of bolus 5-FU, infusional 5-FU should be the 5-FU regimen of choice wherever possible)
- Capecitabine (provided that patients are given clear instructions about the onset of diarrhea and renal function guidelines are obeyed).
- Bolus/infusional 5-FU in combination with oxaliplatin (FOLFOX), although no data are available for the over 75s.

Most importantly, the therapeutic decisions with regard to the choice and duration of adjuvant therapy should be reached jointly by patient and physician, taking into account individual preferences and coexistent comorbidities. Age on the other hand may well be an issue for those >75 years of age.

**Metastatic disease.** The efficacy of 5-FU has been clearly demonstrated in the treatment of the elderly CRC cancer patient, in a historical study versus best supportive care [87] and in a detailed retrospective analysis of 22 phase II and III trials which identified 629 patients >70 years of age [2]. The latter analysis showed fit, elderly patients, with CRC, to benefit from 5-FU therapy to the same extent as younger patients, and confirmed that infusional regimens were more effective than bolus 5-FU regimens. Again in a retrospective review of treatment outcomes in the palliative setting, older and younger patients were shown to exhibit similar efficacy in terms of response, relapse-free survival and 1-year survival, but with a slight reduction in OS (P = 0.04) [84]. Univariate and multivariate analyses on the basis of the individual data from 602 patients, included in two phase III trials of irinotecan therapy (one in the first line the other in the second line setting), to determine predictive factors of survival in metastatic CRC (mCRC), showed irinotecan-based therapy to be independently associated with improved survival and age not to be a prognostic factor [88]. More recently, a multivariate analysis including treatment and age was carried out using the data from the 5-FU/FA and 5-FU/FA/irinotecan arms of three randomized studies [89–91] conducted between 1996 and 2001 [92]. Patients were divided into two groups: elderly (≥70 years, n = 249) and nonelderly (<70 years, n = 1010). Analysis of the toxicity data for the two groups showed the toxicity to be generally comparable between the two age groups, with the exception of a marginally higher incidence of severe neutropenia, grade 3 or more, in elderly patients who received 5-FU/FA alone. This difference was not seen for patients who received 5-FU/FA/irinotecan. A trend toward an unfavorable OS during the first weeks of treatment in elderly patients in the irinotecan arm who received bolus (IFL), but not infusional, 5-FU (FOLFIRI and variants) was observed. Overall, the toxicity was broadly similar for the elderly and nonelderly patients while the efficacy data suggested that elderly patients were as likely to benefit from 5-FU/FA/irinotecan therapy as younger patients. Meanwhile, a pooled safety and efficacy analysis of FOLFOX4 in elderly (≥70 years) compared with younger patients with CRC in the adjuvant [6], first-line [93, 94] and second-line [95] settings showed FOLFOX4 to maintain its efficacy and safety ratio in selected elderly CRC patients [85]. In this analysis, only 16% of the patients enrolled into the trials were ≥70 years old and the data for patients over the age of 80 using this regimen are scant. Thus, with careful monitoring for toxicity and rapid intervention, there is probably no reason why elderly patients should not receive either irinotecan-based or oxaliplatin-based therapy unless other contraindications for chemotherapy exist. Other combination therapy studies support this conclusion [96–98]. More recently, randomized data from studies specifically designed to assess the role of single agent versus combination chemotherapy in the elderly CRC patient have been reported in abstract form and give additional useful information on patterns of toxicity and efficacy in the metastatic setting [99, 100]. The Medical Research Council in UK assessed the use of 5-FU or capecitabine with or without oxaliplatin in ‘elderly and frail’ patients using a 2 × 2 factorial design and some of the conclusions were that: (i) such a trial is feasible in the elderly, (ii) the strategy of starting with an initial 80% dose appears successful, (iii) substituting capecitabine for 5-FU produced significantly higher grades 3–4 toxic effects and (iv) that this group of patients have a markedly reduced OS as compared with the ‘standard’ RCT populations. Mitry and colleagues randomized patients to receive 5-FU with or without irinotecan and concluded that such a phase III trial is feasible in elderly patients with metastatic CRC and that patients aged >75 can be treated with standard chemotherapy regimens with manageable toxicity.

Limited data from studies of the two targeted therapies approved for use in the treatment of CRC, namely bevacizumab [101, 102] and cetuximab [103, 104], suggest that they are probably safe in an elderly population. However, bevacizumab, in particular, has a side-effect profile that includes hypertension (the most frequent side-effect), proteinuria, thromboembolic events, bleeding, wound healing complications and bowel perforation which need careful consideration when treating elderly CRC patients [101, 102, 105, 106]. In particular, arterial thromboembolic events following bevacizumab were more likely to occur in patients >65 years of age or who had a previous history (>18%) of such events. Apart from a higher rate of arterial thromboembolic events, recent data from the BRITe study suggest that safety data in the elderly is comparable to that in patients younger than 65 years. The available data, although limited, suggest that cetuximab both alone and in combination is safe and active in ‘fit’ elderly patients with CRC both first- and second-/subsequent line and that cetuximab monotherapy [103, 107–110] might be an option for those patients who are not candidates for chemotherapy in either the first- or subsequent-line settings. Clearly, more data are required.

In patients with a mean age of 62 years, the anti-epidermal growth factor receptor (EGFR) agent panitumumab has been shown to prolong progression-free survival in previously treated mCRC patients [111]. Recent data have clearly demonstrated that anti-EGFR agents should be only
offered to patients whose tumors are wild-type K-RAS.
Those patients with tumors in which K-RAS mutation is present do not benefit from anti-EGFR therapy [112].

**palliative versus curative therapy in the elderly**

Despite the recent advances in first-line chemotherapy strategies for the treatment of patients with advanced CRC, liver resection offers the only chance of long-term survival or even cure for patients with colorectal liver metastases. Over the past 5 years, there has been the recognition that preoperative, neo-adjuvant, combination chemotherapy regimens can facilitate the downsizing of colorectal liver metastases and render initially unresectable metastases resectable [113–116] and that the addition of targeted therapies [102, 117–122] or a third cytotoxic to these standard combination therapy regimens [123–126] might render them even more effective in this clinical setting. However, almost no elderly patients have been included in the trials of preoperative chemotherapy. Certainly the tolerance of the elderly patient to the triplet cytotoxic chemotherapy regimen that is emerging as one of, if not the most active chemotherapy regimen in this treatment setting [124], needs to be investigated further. Preoperative chemotherapy is also associated with increased postoperative morbidity [127, 128]. A recent retrospective report from the LiverMetSurvey registry suggests that well-selected elderly patients may benefit from liver metastasectomy, with 5-year survival of ~37% [129]. Perioperative mortality was increased, however, for this group of patients.

The precise role of neo-adjuvant chemotherapy for the resection of initially unresectable liver metastases is still emerging for the younger patients recruited into trials and the treatment choices are likely to be more critical for elderly patients. So the question for elderly patients is ‘should we do everything to facilitate hepatic resection by exposing patients to intensive preoperative chemotherapy or opt for palliative chemotherapy and keep an open mind about surgery depending on response?’

**recommendations.**

- Fit elderly patients do benefit from systemic chemotherapy
- 5-FU continuous infusion is more effective and less toxic than bolus 5-FU
- Combination chemotherapy should be the treatment of choice with or without bevacizumab.
- For capecitabine, dose reduction according to creatinine clearance is necessary.
- Cetuximab and panitumumab should be used within the context of their licensed indication. Although data for the use of these agents in the treatment of elderly patients are lacking, it is unlikely that they have a different tolerance in elderly compared with younger patients.

**overall conclusions and recommendations going forward**

As a consequence of the underrepresentation of elderly patients in clinical trials and despite the fact that patients >70 years of age represent half of all CRC patients, our knowledge of the performance of the appropriate therapeutic strategies in this age group is often severely limited [130–132]. The low rate of inclusion, ranging from one-quarter to one-third of potentially eligible elderly patients in chemotherapy trials, can be due to a range of factors. The most common barriers reported in one literature review were physician’s perceptions and protocol eligibility criteria (predetermined subject age limits, restrictions on comorbid conditions and functional status requirements to optimize treatment tolerability). Other barriers were logistical relating to the lack of social support for elderly patients and the extra time needed for patient enrollment. For similar reasons, this lack of access to treatment for eligible elderly patients presumably also extends to those treated outside clinical trials in community settings. It is fair to say that the oncology community has yet to conduct appropriate dose optimization trials in the elderly. Therefore, we are currently ill equipped to select appropriate doses with predictable and acceptable levels of toxicity for this group of patients. The SIOG recommendations for the management of the elderly CRC cancer patient are listed below.

**recommendations.**

- It is important to establish an overall treatment plan for the management of elderly CRC patients.
- Elderly patients should receive screening and earlier diagnosis.
- Elderly patients should be exposed to more aggressive management than they are currently receiving which is closer to that currently received by younger patients.
- Patients should receive the most intensive and appropriate treatment thought to be safe and effective according to their biological age and comorbidities.
- The aim should be to maximize OS while minimizing toxicity to achieve the greatest patient benefit.
- There is, as in younger patients, a need to identify the right patient for the right treatment (pharmacogenetics, pharmacogenomics, etc.).

Looking to the future, a shift in clinical CRC practice and trial design is needed, which will involve bringing CGA into clinical practice with a view to tailoring treatment to the actual patients and patient populations that are present in the clinic.

**acknowledgements**

The preparation of these guidelines was supported by Pfizer and the initial draft was prepared by an agency. All authors reviewed this manuscript. They contributed to the originating meeting, the revisions and the final draft. D. Papamichael was the leader of this work.

**references**


