supportive care alone in patients with metastatic colorectal cancer. *Br Med J* 1993, **306**, 752–755.
35. Stein BN, Petrelli NJ, Douglass HO, *et al.* Age and sex are independent predictors of 5-fluorouracil toxicity. Analysis of a large scale phase III trial. *Cancer* 1995, **75**, 11–17.
36. Petrelli N, Douglass Jr HO, Herrera L, *et al.* The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma: a prospective randomized phase III trial. Gastrointestinal Tumor Study Group. *J Clin Oncol* 1989, **7**, 1419–1426.
37. Popescu RA, Norman A, Ross PJ, *et al.* Results and toxicity of adjuvant and palliative chemotherapy for colorectal cancer (CRC) in elderly patients. *Br J Cancer* 1998, **78**, P01.
38. Cascinu S, Del Ferro E, Catalano G. Toxicity and therapeutic response to chemotherapy in patients aged 70 years or older with advanced cancer. *Am J Clin Oncol* 1996, **19**, 371–374.
39. Pazdur R, Zinner R, Rothenberg ML, *et al.* Age as a risk factor in irinotecan (CPT-11) treatment of 5-FU refractory colorectal cancer. *Proc Am Soc Clin Oncol* 1997, **16**, 260a.
40. Simoni C, Chiara S, Nobile MT, *et al.* Analysis of toxicity and efficacy of chemotherapy in elderly patients with advanced colorectal cancer. *Ann Oncol* 1998, **9**(Suppl. 3), 82.
41. Wils J, Sahmoud T, Sobrero A, *et al.* Evaluation of clinical efficacy of new medical treatments in advanced colorectal cancer. Results of a workshop organized by the EORTC GITCCG. *Tumori* 1998, **84**, 335–347.
42. Lokich JJ, Ahlgren JD, Gullo JJ, *et al.* A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. *J Clin Oncol* 1989, **7**, 425–432.
43. De Gramont A, Bosset JF, Milan C, *et al.* Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French intergroup study. *J Clin Oncol* 1997, **15**, 808–815.
44. Cunningham D. Mature results from three large controlled studies with raltitrexed ('Tomudex'). *Br J Cancer* 1998, **77**, 15–21.
45. Balducci L. Cancer and age. *Forum Trends Exp Clin Med* 1994, **4**, 554–565.
46. Lipschitz DA, Udupa KB. Age and the hematopoietic system. *J Am Geriatr Soc* 1986, **34**, 448–454.
47. Lipschitz DA. Age-related declines in hematopoietic reserve capacity. *Semin Oncol* 1995, **22**(Suppl. 2), 3–5.
48. Rothstein G. Hematopoiesis in the aged: a model of hematopoietic dysregulation? *Blood* 1993, **82**, 2601–2604.
49. Zagonel V, Fratino L, Sacco C, *et al.* Reducing chemotherapy-associated toxicity in elderly cancer patients. *Cancer Treat Rev* 1996, **23**, 223–244.
50. Findlay MP, Griffin AM, Raghavan D, *et al.* Retrospective review of chemotherapy for small cell lung cancer in the elderly: does the end justify the means? *Eur J Cancer* 1991, **27A**, 1597–1601.
51. Milano G, Etienne MC, Cassuto-Viguier E, *et al.* Influence of sex and age on fluorouracil clearance. *J Clin Oncol* 1992, **10**, 1171–1175.
52. Port RE, Daniel B, Ding RW, *et al.* Relative importance of dose, body surface area, sex, and age for 5-fluorouracil clearance. *Oncology* 1991, **48**, 277–281.
53. Chiara S, Nobile MT, Vincenti M, *et al.* Advanced colorectal cancer in elderly patients: results of consecutive trials with 5-FU based chemotherapy. *Proc Am Soc Clin Oncol* 1997, **16**, 272a.
54. Grem JL, Jordan E, Robson ME, *et al.* Phase II study of fluorouracil, leucovorin, and interferon alfa-2a in metastatic colorectal carcinoma. *J Clin Oncol* 1993, **11**, 1737–1745.
55. Bonadonna G, Valagussa P. Dose-response effect of adjuvant chemotherapy in breast cancer. *N Engl J Med* 1981, **304**, 10–15.
56. Budman DR, Berry DA, Cirrincione CT, *et al.* Dose and dose intensity as determinants of outcome in the adjuvant treatment of breast cancer. The Cancer and Leukemia Group B. *J Natl Cancer Inst* 1998, **90**, 1205–1211.
57. Tannock IF, Boyd NF, DeBoer G, *et al.* A randomized trial of two dose levels of cyclophosphamide, methotrexate, and fluorouracil chemotherapy for patients with metastatic breast cancer. *J Clin Oncol* 1988, **6**, 1377–1387.
58. Cunningham D, Zalcberg JR, Rath U, *et al.* 'Tomudex' (ZD1694): results of a randomised trial in advanced colorectal cancer demonstrate efficacy and reduced mucositis and leucopenia. The 'Tomudex' Colorectal Cancer Study Group. *Eur J Cancer* 1995, **31A**, 1945–1954.
59. Abad A, Navarro M, Sastre J, *et al.* Phase II continuous UFT plus folinic acid in elderly patients with colorectal cancer. *Proc Am Soc Clin Oncol* 1997, poster 994.
60. Anderson H, Palmer MK. Measuring quality of life: impact of chemotherapy for advanced colorectal cancer. Experience from two recent large phase III trials. *Br J Cancer* 1998, **77**(Suppl. 2), 9–14.
61. Redmond K. Assessing patients' needs and preferences in the management of advanced colorectal cancer. *Br J Cancer* 1998, **77**(Suppl. 2), 5–7.
62. International Working Group on Colorectal Cancer. An international multidisciplinary approach to the management of advanced colorectal cancer. *Eur J Surg Oncol* 1997, **23**(Suppl. A), 4–66.
63. Medical Research Council. *MRC Topic Review: The Health of the UK's Elderly People*. London, MRC, 1994.
64. Stiggelbout AM, de Haes JC, Kiebert GM, *et al.* Tradeoffs between quality and quantity of life: development of the QQ Questionnaire for Cancer Patient Attitudes. *Med Decision Making* 1996, **16**, 184–192.
65. Uhlmann R, Pearlmann R. Perceived quality of life and preferences for life sustaining treatment in older adults. *Arch Int Med* 1991, **151**, 495–497.
66. Balducci L. Perspectives on quality of life of older patients with cancer. *Drugs Aging* 1994, **4**, 313–324.

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In Western Europe, a quarter of the population is aged over 70 years, with a predicted increase to one-third of the population over the next two decades [1]. Improvements in healthcare combined with a falling birth rate have resulted in the older population increasing twice as rapidly as the total population. The majority of cancers occur in the elderly population, but until recently relatively little consideration has been given to treatment of cancer in the older patient.

Colorectal cancer is the second most frequent cause of cancer death with approximately 165 000 deaths per annum

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in both the European Union and the U.S.A. [2]. The incidence of colorectal cancer rises steeply during the seventh and eighth decades. In the U.K., the incidence rate is three times higher in people aged over 80 years compared with those aged 60 years. In a sample of 75 266 US Medicare beneficiaries in 1987, the incidence was 3.87 per 1000 in those aged 85 years or over compared with 1.59 per 1000 in those aged 65–69 years [3]. Already two-thirds of colorectal cancer in women and over half in men occurs in subjects aged 70 years or over [4]. The proportion of cases occurring in patients over 70 years will rise with the anticipated demographic changes.

Increased awareness of the implications of the demographic changes occurring has focused attention on the management of colorectal cancer in the elderly [5, 6]. These studies have demonstrated that older patients are less commonly adequately investigated for potential cancer symptoms and incompletely staged following a diagnosis of colorectal cancer. Increased access to colonoscopy since the mid-1970s has resulted in improvements for all patients, but particularly the elderly. Consequently, the proportion of patients diagnosed at an earlier stage has increased, with higher rates of curative surgery.

Despite progress in diagnosis and surgery of patients, 60% ultimately die from advanced colorectal cancer. The survival and quality of life benefits of chemotherapy for advanced colorectal cancer were established in randomised comparisons with best supportive care [7–10]. However, patients over the age of 70 years received chemotherapy less frequently than younger patients [5]. The most likely explanation is the failure of surgeons and physicians to refer patients for chemotherapy due to its perceived toxicity and an alleged higher side-effect profile in older patients. Moreover, many clinical trials evaluating new cytotoxic agents for the treatment of colorectal cancer continue to exclude older patients, particularly patients over the age of 75 years. In trials permitting participation of older patients they remain underrepresented, and few studies present an analysis based on different age cohorts of participating patients [11].

Patients' suitability for chemotherapy should be based on an assessment of performance status and an arbitrary age cut-off is unjustified. Patients who maintain a European Clinical Oncology Group (ECOG) performance status of 0, 1 or 2 should be considered for chemotherapy, whereas, patients with an ECOG performance status of 3 or 4 have an unfavourable risk: benefit ratio from treatment with chemotherapy. Due to a higher incidence of comorbid conditions fewer older patients may be suitable for chemotherapy. However, until oncologists review all patients with advanced colorectal cancer it is impossible to know the proportion of patients over 70 years who should be offered chemotherapy.

It is time to review the perception that toxicity of chemotherapy is worse in older patients. One study evaluating four different regimens of bolus 5-fluorouracil and leucovorin did demonstrate a higher incidence of severe toxicity in patients over the age of 70 years [12]. However, this trial recruited patients between 1984 and 1987. A recently published retrospective analysis of patients treated in prospective trials demonstrated no significant differences in toxicity between those 65 years or older compared with younger patients [13]. In these trials, patients were treated with either weekly bolus 5-fluorouracil alone or in combination with leucovorin or with weekly 24-h high-dose infusional 5-fluorouracil plus leucovorin. Increasingly in major European oncology centres 5-fluorouracil is being administered as a continuous infusion either alone or in combination with leucovorin. Two of these regimens, the 48-h bimonthly schedule of 5-fluorouracil plus leucovorin, and protracted venous infusion 5-fluorouracil have demonstrated improved toxicity profiles compared with bolus 5-fluorouracil regimens [14, 15]. Data from the Gastrointestinal Unit of the Royal Marsden Hospital have found no differences in either overall or severe common toxicity criteria (CTC) grades 3/4 toxicity in patients 70 years or older compared with younger patients treated with chemotherapy for advanced colorectal cancer [16]. In addition, response rates and failure-free survival were similar in the two cohorts. Median overall survival was inferior in patients 70 years or older ($P = 0.04$), with 1-year survival 44% compared with 48% in younger patients.

Two phase II studies have evaluated oral 5-fluorouracil analogues in patients of 70 years or older [17, 18]. One study including 42 patients treated with doxifluridine observed a response rate of 14%, with median progression-free and overall survival times of 13 and 40 weeks, respectively. The other study included 38 patients treated with UFT plus leucovorin. This study reported a response rate of 29% with overall survival of 12.5 months. Moreover, response was not related to age (70–75 years versus >75 years) but there was a trend toward a significant association between response and performance status (0, 1 versus 2). In both studies diarrhoea was the most frequent toxicity with 16 and 10% incidence, respectively, with World Health Organisation (WHO) grade 3/4 diarrhoea. Neither study reported any toxic deaths. No association between grade 3/4 toxicity and age (70–75 years versus >75 years) or ECOG performance status was observed. Thus, based on all the available data patients aged 70 years or older of good performance status tolerate first-line fluoropyrimidine-based treatment for advanced colorectal cancer and have similar outcomes to younger patients.

Recently, the survival and quality of life advantages of second-line chemotherapy in patients with 5-fluorouracil resistant colorectal cancer have been demonstrated [19]. In comparison with best supportive care, overall survival was significantly better with irinotecan ($P = 0.0001$), and 1-year survival improved from 14% with supportive care to 36% with irinotecan. The survival benefits of irinotecan were observed in all performance status groups (<2 or =2), although the prognosis for patients with performance status 0 and 1 was better than that for patients with performance status 2. In addition, patients treated with irinotecan had fewer tumour-related symptoms and a better quality of life when treated with irinotecan than with supportive care alone. Furthermore, irinotecan demonstrated a survival advantage compared with infusional 5-fluorouracil as second-line therapy. Patients aged over 75 years were ineligible for these trials and no sub-group analysis for patients aged 70–75 years were presented. However, on the strength of these results patients aged 70–75 years and of good performance status should be offered second-line chemotherapy. No clear recommendations can be made for patients aged over 75 years, but clearly each case should be considered individually.

In conclusion, the number of elderly patients with advanced colorectal cancer is anticipated to rise as a consequence of an ageing population. Despite progress in the staging and diagnosis that has been particularly beneficial for elderly patients, approximately 60% ultimately die of colo-

rectal cancer. Patients over 70 years show similar benefits from palliative chemotherapy to younger patients, without any difference in toxicity profiles. Thus, patients over the age of 70 years maintaining a good performance status should be offered chemotherapy.


1. Furner SE, Brody JA, Jankowski LM. Epidemiology and aging. In Cassel CK, Cohen HJ, Larson EB, *et al.*, eds. Geriatric medicine, 3rd edn. New York, Springer, 1997, 37–43
2. Cancer of the large bowel—UK. *Cancer Research Factsheet* 1993 (18.1).
3. Cooper GS, Yuan Z, Landefeld CS, *et al*. A national population-based study of incidence of colorectal cancer and age. Implication for screening in older Americans. *Cancer* 1995, **75**, 775–781.
4. Fentiman IS, Tirelli U, Monfardini S, *et al*. Cancer in the elderly: why so badly treated? *Lancet* 1990, **335**, 1020–1022.
5. de Rijke JM, Schouten LJ, Schouten HC, Jager JJ, Koppejan AG, van den Brandt PA. Age-specific differences in the diagnostics and treatment of cancer patients aged 50 years and older in the province of Limburg, The Netherlands. *Ann Oncol* 1996, **7**, 677–685.
6. Arveux I, Boutron MC, El Mrini T, Arveux P, Pfitzenmeyer P, Faivre J. Colon cancer in the elderly: evidence for major improvements in health care and survival. *Br J Cancer* 1997, **76**, 963–967.
7. Scheithauer W, Rosen H, Kornek G-V, Sebesta C, Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *Br Med J* 1993, **306**, 752–755.
8. The Nordic Gastrointestinal Tumor Adjuvant Therapy Group. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomised trial. *J Clin Oncol* 1992, **10**, 904–911.
9. Beretta G, Bollina R, Martignoni G, Morabito M, Tancini G, Villa E. Fluorouracil + folates (FUFO) as standard treatment for advanced/metastatic gastrointestinal carcinoma (AGC). *Ann Oncol* 1994, **5**(Suppl. 8), 239 (abstract).
10. Allen-Mersh TG, Earlam S, Fordy C, Abrams K, Houghton J. Quality of life and survival with continuous hepatic-artery floxuridine infusion for colorectal liver metastases. *Lancet* 1994, **344**, 1255–1260.
11. Trimble EL, Carter CL, Cain D, Freidlin B, Ungerleider RS, Friedman MA. Representation of older patients in cancer treatment trials. *Cancer* 1994, **74**, 2208–2214.
12. Stein BN, Petrelli NJ, Douglass HO, Driscoll DL, Arcangeli G, Meropol NJ. Age and sex are independent predictors of 5-fluorouracil toxicity. Analysis of a large scale phase III trial. *Cancer* 1995, **75**, 11–17.
13. Chiara S, Nobile MT, Vincenti M, *et al*. Advanced colorectal cancer in the elderly: results of consecutive trials with 5-fluorouracil-based chemotherapy. *Cancer Chemother Pharmacol* 1998, **42**, 336–340.
14. de Gramont A, Bosset J-F, Milan C, *et al*. Randomized trial comparing monthly low-dose leucovorin and fluorouracil bolus with bimonthly high-dose leucovorin and fluorouracil bolus plus continuous infusion for advanced colorectal cancer: a French Intergroup study. *J Clin Oncol* 1997, **15**, 808–815.
15. The Meta-analysis Group in Cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J Clin Oncol* 1998, **16**, 301–308.
16. Popescu RA, Norman A, Ross PJ, Parikh B, Cunningham D. Adjuvant or palliative chemotherapy for colorectal cancer in patients 70 years or older. *J Clin Oncol* 1999, in press.
17. Falcone A, Pfanner E, Ricci S, *et al*. Oral doxifluridine in elderly patients with metastatic colorectal cancer: a multicenter phase II study. *Ann Oncol* 1994, **5**, 760–762.
18. Feliu J, González Barón M, Espinosa E, *et al*. Uracil and tegafur modulated with leucovorin. An effective regimen with low toxicity for the treatment of colorectal carcinoma in the elderly. *Cancer* 1997, **79**, 1884–1889.
19. Cunningham D, Pyrhönen S, James RD, *et al*. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet* 1998, **352**, 1413–1418.