Journal of Clinical Gerontology & Geriatrics 6 (2015) 95–99

Contents lists available at ScienceDirect

Journal of Clinical Gerontology & Geriatrics

journal homepage: www.e-jcgg.com

Original article

Retrospective analysis of efficacy and safety of third-line chemotherapy for metastatic colorectal cancer among elderly patients receiving targeted therapy in early lines

Ravit Geva, MD [a, *], Nadav Sarid, MD [b], Einat Shacham-Shmueli, MD [c]

[a] Department of Oncology, Gastrointestinal Tract Malignancies Center, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[b] Department of Hematology, Tel Aviv Sourasky Medical Center, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[c] Department of Gastrointestinal Oncology, Cancer Center, Sheba Medical Center, Tel HaShomer, Israel

ARTICLE INFO

Article history:
Received 28 September 2014
Received in revised form
13 January 2015
Accepted 9 February 2015
Available online 15 July 2015

Keywords:
elderly patients
metastatic colorectal cancer
third-line chemotherapy

ABSTRACT

Background/Purpose: About one-half of metastatic colorectal cancer (MCRC) patients are ≥70 years of age. There is uncertainty regarding the benefit patients derive from advanced chemotherapy lines. In this study, we aim to evaluate the efficacy and safety of third-line chemotherapy treatments among MCRC patients.

Methods: Consecutive patients 70 years or older at the time of diagnosis of metastatic disease who received third-line chemotherapy at the Tel-Aviv Sourasky Medical Center between the years 2000–2009 were collected. Data on demographics, stage of disease, treatment lines and oncological outcomes were extracted from their medical files.

Results: Only 34 out of 63 patients (54%) available patients received third-line treatments. The (median) age of all patients, third-line patients and the remaining patients, were similar (74.5, 74 and 75.3 years, respectively, P = NS). Following third-line treatments, only 9% had a partial response, and the disease was stable in 29% of patients seen. Thirteen weeks is the median duration of third-line treatments. Only three patients had symptomatic relief. Importantly, 15 patients (44%) required dose reduction or treatment delay due to toxicity (neutropenia or thrombocytopenia). The median survival (mOS) is 9 months for patients with first-line treatment, 19 months for second-line treatment and 37 months for third-line treatment (Log Rank < 0.0001). There was a significant association between the number of lines of treatment and the mOS ($P = 0.0001$).

Conclusion: Third-line chemotherapy treatment of elderly MCRC patients was associated with a minor clinical response, a considerable number of side effects, but a longer survival rate. Third-line chemotherapy in fit elderly patients should be pursued, however, protocols must be adjusted before third-line treatment is implemented.

1. Introduction

Colorectal cancer (CRC) is the fourth most commonly diagnosed cancer in men and women, with >1,200,000 new cases detected each year and >600,000 deaths/y worldwide.[1] Approximately one half of the patients are aged ≥ 70 years. Survival of patients has improved considerably in the last 2 decades. As the world population ages, a greater number of elderly patients will require treatment. One fifth to a quarter of all newly diagnosed patients have Stage 4 disease, whereas one third of all early stage patients will develop recurrent metastatic disease. The goals of chemotherapy for patients with metastatic CRC (MCRC) are to

* Corresponding author. Department of Oncology, Gastrointestinal Tract Malignancies Center, Tel Aviv Sourasky Medical Center, 6 Weizman Street, Tel Aviv 6423906, Israel.
E-mail address: ravitg@tlvmc.gov.il (R. Geva).

http://dx.doi.org/10.1016/j.jcgg.2015.02.006

prolong their survival, control their symptoms, and maintain and improve patients' quality of life. Palliative chemotherapy is now offered to an increasing proportion of patients with advanced MCRC. There is no universally accepted standard therapy or route of administration as such, and the current main treatment for metastatic disease is systemic chemotherapy, with or without, a biologically targeted agent. This treatment yields a median survival of 2–3 years.[1,2]

There is some uncertainty regarding the benefits elderly patients receive from adjuvant or palliative chemotherapy, and the extent to which it should be used.[3–5] There are many factors that influence treatment decisions, such as performance status, comorbidity, family or social support, mental status and compliance, physiologic age, and others.[3,4,6] Older patients are also more prone to develop treatment-related toxicity, especially myelotoxicity.[3,4,6]

Moreover, patients who are aged ≥ 70 years typically do not exceed 15–20% of the studied populations in clinical trials, making it difficult to extrapolate the results of these trials when solely applying them to older patients.

Patients with MCRC will be given a greater number of treatment lines the longer they survive. There is a large body of evidence regarding the treatment of elderly MCRC patients in the adjuvant setting[3,4,6] and with first- and second-line treatments[4,5] for metastatic disease. This analysis was aimed to retrospectively evaluate the efficacy and safety of third-line treatments for MCRC among patients aged ≥ 70 years.

2. Methods

2.1. Study population

The study population included consecutive MCRC patients who were aged ≥ 70 years at the time of diagnosis of metastatic disease and those who received third-line chemotherapy treatments at the Tel Aviv Sourasky Medical Center between 2000 and 2009. Data on patients' age, sex, stage of disease, and treatment at the initial diagnosis stage were retrospectively extracted from their medical files. The data pertaining to treatment for metastatic disease included regimens of chemotherapy used for the three different lines of treatment, duration of treatment in weeks, and whether or not there were interruptions in treatment. The response to treatment was evaluated using Response Evaluation Criteria in Solid Tumor 0.1 (RECIST 0.1). Symptom relief and side effects were also recorded from the patients' medical files. Overall survival was calculated from the first diagnosis of the existing metastatic disease.

The Charlson Comorbidity Index[7] was used to score the patients' comorbidity, which was calculated from the patients' medical records, after exclusion of the diagnosis of colorectal carcinoma.

The Charlson Comorbidity Index is the most frequently used comorbidity scoring system in clinical trials. It was initially constructed from a longitudinal analysis of 559 individuals admitted to a medical service.[7] Twenty associated conditions, shown to have a 1-year relative risk of death, were given a weighted value relative to their potential impact. This index has been validated for predicting major complications in many malignancies, including patients with CRC.[8,9]

2.2. Statistical analysis

Parameters of survival were analyzed using Cox regression and demonstrated by Kaplan–Meier curves. Associations between median survival times of various subgroups were analyzed using the Mann–Whitney test. Statistical analyses (statistical significance was defined by an alpha of 0.05) were performed using SPSS software (SPSS Inc., Chicago, IL, USA).

3. Results

A total of 63 consecutive MCRC patients who were aged ≥ 70 years were included in this trial. Most of them (n = 57, 90%) received at least first-line treatments, 45 (71%) received second-line treatments, and 34 (54%) received third-line treatments. The (median) age of all patients, patients receiving third-line chemotherapy treatments, and the remaining patients was 74.5 years, 74 years, and 75.3 years, respectively (p = not significant). Of the total study patients, 38 (60%) were men and 25 (40%) were women. More male patients than female patients received third-line treatments (68% vs. 32%, respectively; $p < 0.05$). Characteristics of the patients are summarized in Table 1. The decrease in treated populations across the different lines of treatment is depicted in Fig. 1.

3.1. Stage of disease at first diagnosis

Seventy-one percent of patients had Stage 4 disease at first diagnosis. There was no significant association between the stage at first diagnosis and the probability of receiving third-line treatment.

3.2. First-line treatment for metastatic disease

The treatment lines used for the 57 patients who received first-line treatments for MCRC are described in Table 2. There was no association between the medication that was administered for the first-line treatment and that used for third-line treatment. The median treatment duration for the whole group was 20 weeks. The median duration of first-line treatment was longer among patients who went on to receive third-line treatments compared with those who did not receive third-line treatments (23 weeks vs. 12 weeks, respectively, $p < 0.05$).

Twenty-five of the 57 patients (44%) who received first-line treatments were given an irinotecan-based regimen, 12 patients (21%) were given an oxaliplatin-based regimen, and 22 patients (39%) received an additional targeted therapy (mainly bevacizumab). There was no association between the first-line treatment regimen and the probability of receiving third-line treatment. Response to treatment was evaluated in 44 patients: it was partial for 13 patients (30%, from evaluated patients), the condition remained stable in 12 patients (27%), and there was disease progression in 19 patients (43%). There was no significant association between the response to first-line treatments and subsequent second- or third-line treatments, although numerically, more patients who responded to the first-line treatments received third-line treatments, compared with those whose disease progressed after their first-line treatment. The median duration of first-line treatments was 20 weeks, and it was longer among patients who later received third-line treatments compared with those who did not receive third-line treatments (21 weeks vs. 12 weeks, respectively, $p = 0.0347$).

3.3. Second-line treatment for metastatic disease

Forty-five patients (71%) received second-line treatments that consisted of an irinotecan-based regimen (16 patients, 36%), an oxaliplatin-based regimen (21 patients, 47%), or an additional targeted therapy (14 patients, 31%). There was no association between the second-line treatment regimen and the probability of receiving third-line treatments. Therapeutic response was evaluated in 31

Table 1
Patients characteristics.

	No. of patients	Median age at diagnosis (y)	Sex of the patient, *n* (%)	Stage at first diagnosis, *n* (%)	CCI, *n* (%)
All patients	63	74.5	Male, 38 (60) Female, 25 (40)	Stage 4, 45 (70)	CCI 0, 29 (46) CCI 1, 21 (33%) CCI 2, 9 (15) CCI 3, 4 (6)
Third-line-treated patients	34	74	Male, 26 (76) Female, 8 (24)	Stage 4, 27 (79) Stage 3, 3 (9) Stage 2, 3 (9) Stage NA, 1 (3)	CCI 0, 15 (44) CCI 1, 14 (41) CCI 2, 4 (12) CCI 3, 1 (3)
No third-line treatment	29	75.3	Male, 12 (41) Female, 17 (59)	Stage 4, 18 (62) Stage 3, 6 (21) Stage 2, 5 (17)	CCI 0, 14 (48) CCI 1, 7 (24) CCI 2, 5 (18) CCI 3, 3 (10) (10)

CCI = Charlson Comorbidity Index; NA = not available.

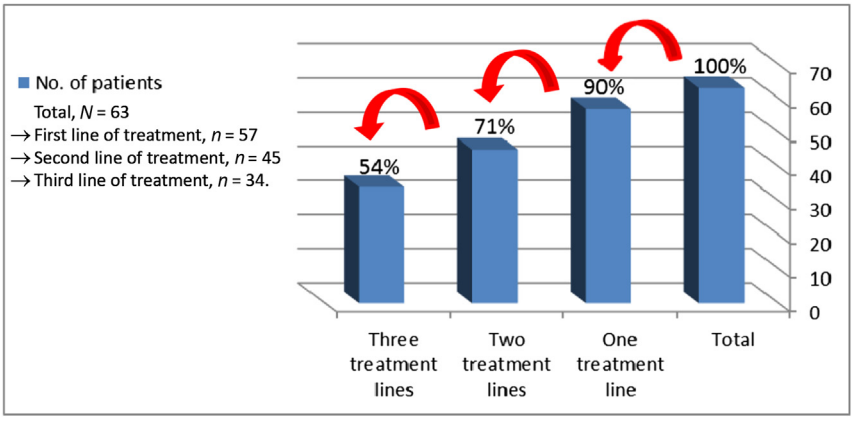

Fig. 1. Percentage of patients across the different treatment lines. The data presented show a decrease from 90% at the first line to 71% and 54% in the second and third lines, respectively.

patients: it was partial in three patients (10%, from evaluated patients), the disease remained stable in 15 patients (48%), and there was disease progression in 13 patients (42%). There was no significant association between the response to the second-line treatment and patients who received third-line treatments later on, although numerically, more patients who responded to the second-line treatment received third-line treatments compared with those patients whose disease progressed on their second-line treatment. The median duration of second-line treatment was 18 weeks, and it was longer among patients who later received third-line treatments compared with those who did not receive third-line treatments (20 weeks vs. 7 weeks, respectively, $p = 0.0129$).

3.4. Third-line treatment for metastatic disease

A total of 34 patients (54%) received third-line treatments that consisted of an irinotecan-based regimen for 13 patients (38%), an oxaliplatin-based regimen for 11 patients (32%), and an additional targeted therapy for 13 patients (38%). There was no association between the second-line treatment regimen and the probability of receiving third-line treatments. The therapeutic response was evaluated in 29 patients: it was partial in three patients (10%), the disease remained stable in 10 patients (34%, from evaluated patients), and there was disease progression in 16 patients (55%). The median duration of third-line treatment was 13 weeks. Twenty-two patients (65%) were symptomatic at the start of the third-line treatment, 10 patients (29%) were asymptomatic, and there were two patients with missing information. Only three patients had symptomatic relief from third-line treatment. Toxicity of third-line treatments required dose reduction or treatment delays in 15 patients (44%). The most common side effects were general weakness ($n = 23$, 68%), diarrhea ($n = 15$, 44%), and neutropenia ($n = 8$, 24%).

3.5. Survival data

At the time of data collection, eight patients were still alive and three had been lost to follow up. The median survival rate since the first diagnosis was 28 months. Patients who only had first-line treatment had a median survival of 9 months, those with second-

Table 2
Treatment lines combinations.

Treatment line for MCRC	Patients	Oxaliplatin + fluoropyrimidine	Irinotecan + fluoropyrimidine	Fluoropyrimidine only	Chemotherapy + bevacizumab	Chemotherapy + cetuximab
First line	57 (90)	12 (21)	25 (44)	16 (28)	21 (37)	1 (2)
Second line	45 (71)	21 (45)	16 (36)	5 (11)	9 (20)	5 (11)
Third line	34 (54)	11 (32)	13 (38)	6 (2)	2 (6)	11 (32)

Data are presented as *n* (%).
MCRC = metastatic colorectal cancer.

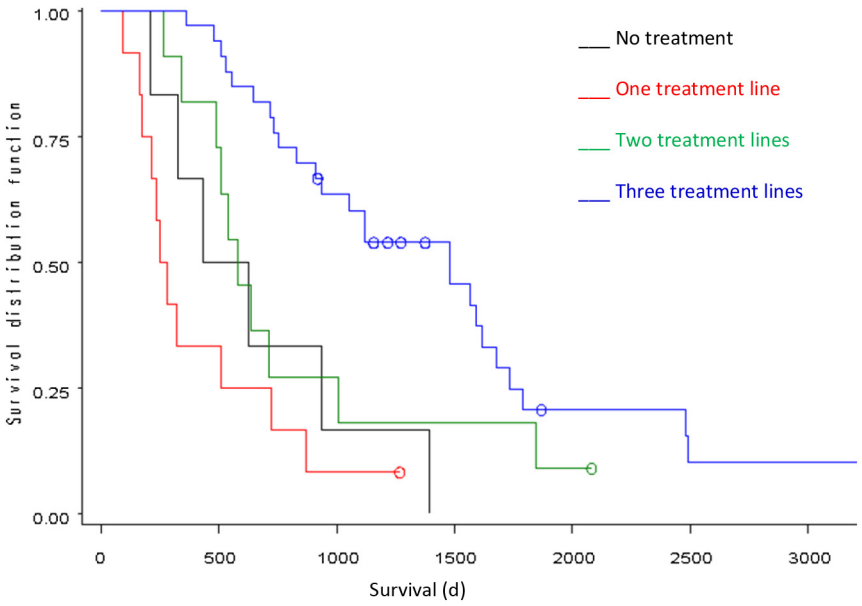

Fig. 2. Overall survival according to the number of treatment lines for metastatic disease. Patients receiving three lines of treatment had clearly better overall survival compared with patients receiving one or two lines of treatment ($p = 0.0001$).

line treatment had a median survival of 19 months, and those who received third-line treatment had a median survival of 37 months (log rank < 0.0001; Fig. 2). The median survival since the first diagnosis of metastases was 23 months. Patients who had received only first-line treatment had a median survival of 7 months, those who were treated with second-line treatment had a median survival of 16 months, and those who received third-line treatment had a median survival of 35 months (log rank < 0.0001; Fig. 2). There was a significant association between the number of treatment lines and median overall survival ($p = 0.0001$). There was also a significant association between the lack of response to the first-line treatment and a worse median overall survival. Patients who had progression of disease during the first-line treatment had a shorter survival rate than patients who had responsive or stable disease ($p = 0.0014$, Fig. 3). There were no differences between the patients' response to the second- and third-line treatments and survival or in the association between the choice of chemotherapy combination and the length of survival.

4. Discussion

The median survival of elderly CRC patients is shorter than that of younger patients.[7] This might be due to a number of reasons, such as comorbidity and decreased performance status. It may also be attributed to the undertreatment of older patients as a group. Jessup et al[9] reported that the use of adjuvant chemotherapy differed considerably by age: adjuvant chemotherapy was used in 82% of patients aged < 60 years, 77.2% of patients aged between 60 years and 69 years, 69% of patients aged between 70 years and 79 years, and only 39.2% of patients aged ≥ 80 years. In addition, Dobie et al[10] noted that when adjuvant chemotherapy was used, the chance of treatment termination before the completion of planned full dose was higher among the elderly patients. This trend of undertreatment of the elderly patients is also evident in the metastatic disease setting, as well as in the use of doublets (irinotecan- or oxaliplatin-based regimens) and triplets (adding a biological agent).[11]

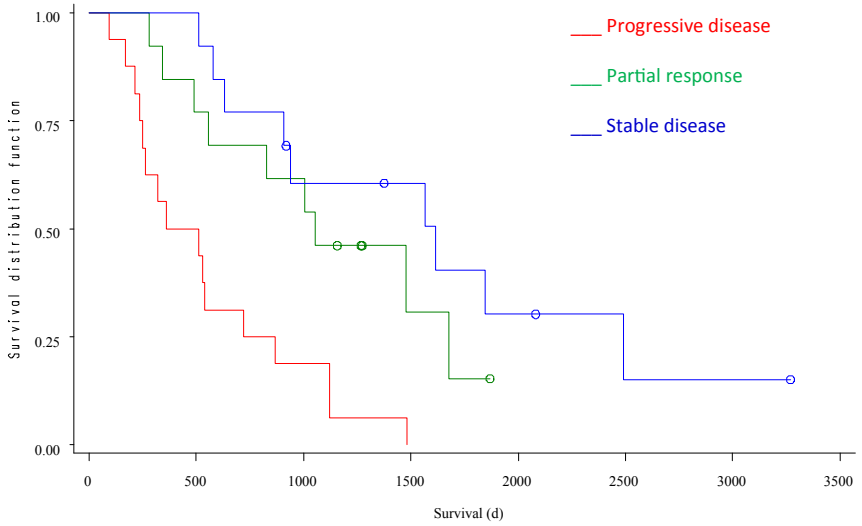

Fig. 3. Overall survival based on the response to first-line treatment. Patients who had progression of disease during first-line treatment had a shorter survival than patients who had responsive or stable disease ($p = 0.0014$).

This retrospective analysis revealed several aspects of MCRC treatment in elderly patients. As expected, the median treatment duration was shortened as more treatment lines were used (20 weeks, 18 weeks, and 13 weeks for first, second, and third line, respectively). The duration of first-line treatment in our analysis was shorter than that reported in the latest data (approximately 30–35 weeks[2]). This might be attributable to both the poor general status of our elderly patient population and the fact that only one third of them were actually treated with targeted agents.

Response to treatment lessened as the treatment lines progressed (partial response of 30%, 10% and 10%, from evaluated patients). The reported response to first-line treatments is usually higher for the general patient population (>40%[1,2]) than the cohort in this study, suggesting a reduced benefit among elderly patients when evaluated in isolation. The question of whether there is a benefit for combination chemotherapy was recently raised by data that reviewed the treatment of elderly patients in both adjuvant and metastatic settings. Sargent et al[3] showed that adjuvant 5-fluorouracil (5FU)-based chemotherapy was an effective adjuvant treatment in elderly patients as well as in younger patients, however, recent publications have raised some concerns regarding administering adjuvant treatments to elderly patients. One of them, the QUick and Simple And Reliable (QUASAR) trial subset analysis of Stage 2 patients, clearly showed no treatment benefit of adjuvant 5FU among elderly patients.[12] The Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, in which the adjuvant folinic acid, 5FU, and oxaliplatin (FOLFOX) was compared with 5FU, showed an overall survival advantage for FOLFOX among the elderly patients until the 4th year of follow up, however, this advantage was lost after a longer follow up.[13] Another trial, in which the adjuvant XELOX (xeloda, oxaliplatin) was compared with 5FU, also demonstrated a questionable beneficial effect of adjuvant treatment in older patients in a subset analysis.[14] The Adjuvant Colon Cancer End Points (ACCENT) meta-analysis clearly demonstrated no beneficial effect of combination adjuvant chemotherapy among 2170 patients who were aged $\geq$ 70 years, even for those in the third stage of disease.[4] As for treatment of elderly MCRC patients with targeted agents, one recent subset analysis of the Cetuximab Combined with Irinotecan in First-line Therapy for Metastatic Colorectal Cancer (CRYSTAL) trial, in which first-line treatment with folinic acid, 5FU, and irinotecan (FOLFIRI) was compared with FOLFIRI + cetuximab, showed no significant benefit in adding cetuximab to patients who were aged $\geq$ 70 years.[15]

Only 14% of our patients who received third-line treatments experienced any symptomatic relief. By contrast, a large proportion of these patients had treatment-related side effects (mainly weakness, diarrhea, and neutropenia). At least one treatment delay, mainly due to general deterioration or bone marrow toxicity (neutropenia or thrombocytopenia), was required in 15 patients (44%). The same number of patients also required dose reduction, mainly due to weakness and diarrhea. These large gaps between low rates of symptomatic relief and high rates of toxicity are worrisome, given that the main goal of treatment in this setting is palliative care.

Our finding that the overall survival rate correlates with the number of treatment lines was expected. This correlation was also well-described by Grothey et al.[1] Likewise, the lack of any correlation between the combinations and sequences of treatments and overall survival had been described by Tournigand et al.[2]

5. Conclusion

The treatment of elderly MCRC patients with third-line chemotherapy was associated with only a minor clinical response but with a considerable number of serious side effects. Thus, treatment should be adjusted for this special population before proceeding to further lines of treatment, especially after the failure of the first-line chemotherapy treatment.

Conflicts of interest

The authors have no conflicts of interest to disclose.

Acknowledgments

The authors thank Esther Eshkol for editorial assistance.

References

1. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 2004;**22**:1209–14.
2. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;**22**:229–37.
3. Sargent DJ, Goldberg RM, Jacobson SD, Macdonald JS, Labianca R, Haller DJ, et al. A pooled analysis of adjuvant chemotherapy for resected colon cancer in elderly patients. *N Engl J Med* 2001;**345**:1091–7.
4. Jackson McCleary NA, Meyerhardt J, Green E, Yothers G, de Gramont A, Van Cutsem E, et al. Impact of older age on the efficacy of newer adjuvant therapies in >12,500 patients (pts) with stage II/III colon cancer: findings from the ACCENT Database. *J Clin Oncol* 2009;**27**:4010 [Meeting Abstract].
5. Goldberg RM, Tabah-Fisch I, Bleiberg H, de Gramont A, Tournigand C, Andre T, et al. Pooled analysis of safety and efficacy of oxaliplatin plus fluorouracil/leucovorin administered bimonthly in elderly patients with colorectal cancer. *J Clin Oncol* 2006;**24**:4085–91.
6. International Agency for Research on Cancer. GLOBOCAN population fact sheet. Lyon, France: IARC. Available at: http://globocan.iarc.fr/Default.aspx. last entry 3/6/2015.
7. Chau I, Norman AR, Cunningham D, Waters JS, Topham C, Middleton G, et al. Elderly patients with fluoropyrimidine and thymidylate synthase inhibitor-resistant advanced colorectal cancer derive similar benefit when treated with irinotecan monotherapy. *Br J Cancer* 2004;**91**:1453–8.
8. Guyot F, Faivre J, Manfredi S, Meny B, Bonithon-Kopp C, Bouvier AM. Time trends in the treatment and survival of recurrences from colorectal cancer. *Ann Oncol* 2005;**16**:756–61.
9. Jessup JM, Stewart A, Greene FL, Minsky BD. Adjuvant chemotherapy for stage III colon cancer: implications of race/ethnicity, age, and differentiation. *JAMA* 2005;**294**:2703–11.
10. Dobie SA, Baldwin LM, Dominitz JA, Matthews B, Billingsley K, Barlow W. Completion of therapy by Medicare patients with stage III colon cancer. *J Natl Cancer Inst* 2006;**98**:610–9.
11. McKibbin T, Frei CR, Greene RE, Kwan P, Simon J, Koeller JM. Disparities in the use of chemotherapy and monoclonal antibody therapy for elderly advanced colorectal cancer patients in the community oncology setting. *Oncologist* 2008;**13**:876–85.
12. Quasar Collaborative Group, Gray R, Barnwell J, McConkey C, Hills RK, Williams NS, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet* 2007;**370**:2020–9.
13. André T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. *J Clin Oncol* 2009;**27**:3109–16.
14. Haller DG, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capecitabine plus oxaliplatin compared with fluorouracil and folinic acid as adjuvant therapy for stage III colon cancer. *J Clin Oncol* 2011;**29**:1465–71.
15. Folprecht G, Köhne CH, Bokemeyer C, Rougier P, Schlichting M, Heeger S, et al. Cetuximab and 1st-line chemotherapy in elderly and younger patients with metastatic colorectal cancer (mCRC): a pooled analysis of the CRYSTAL and OPUS studies. *Ann Oncol* 2010;**21**:597P.