International Journal of Colorectal Disease (2019) 34:1741–1747
https://doi.org/10.1007/s00384-019-03389-w

ORIGINAL ARTICLE

Impact of age on toxicity and efficacy of 5-FU-based combination chemotherapy among patients with metastatic colorectal cancer; a pooled analysis of five randomized trials

Omar Abdel-Rahman[1] · Hatim Karachiwala[1]

Accepted: 1 September 2019 / Published online: 6 September 2019

Abstract

Objective To assess the impact of age on toxicity and efficacy outcomes of metastatic colorectal cancer treated with 5FU-based combination chemotherapy.

Methods Project Data Sphere (PDS) platform has been accessed and de-identified datasets of the following clinical trials were downloaded (NCT00272051; NCT00305188; NCT00115765; NCT00364013; and NCT00384176). Multivariable logistic regression analysis was used to assess the impact of age (< 70 years versus ≥ 70 years) on the probability of different toxicities. Multivariable Cox regression analysis was additionally used to evaluate the impact of age (< 70 years versus ≥ 70 years) on overall and progression-free survival.

Results Among a total of 3223 patients included in the current analysis, 2488 patients were < 70 years; while 735 patients were ≥ 75 years at randomization. Older age was associated with a higher probability of serious adverse events (OR (odds ratio) 0.649; 95% CI 0.545–0.772; $P < 0.001$), fatal adverse events (OR 0.416; 95% CI 0.299–0.579; $P < 0.001$), all-grade diarrhea (OR 0.834; 95% CI 0.699–0.994, $P = 0.043$), high-grade diarrhea (OR 0.734; 95% CI 0.577–0.933, $P = 0.012$), high-grade stomatitis (OR 0.500, 95% CI 0.290–0.861, $P = 0.012$), high-grade thrombocytopenia (OR 0.578; 95% CI 0.359–0.930, $P = 0.024$), all-grade neutropenia (OR 0.690; 95% CI 0.578–0.824, $P < 0.001$), and high-grade neutropenia (OR 0.661; 95% CI 0.549–0.796, $P < 0.001$). In a multivariable Cox regression analysis for factors affecting overall survival, older age was associated with worse overall survival (hazard ratio for younger age versus older age 0.848; 95% CI 0.754–0.954, $P = 0.006$). On the hand, older age was not associated with worse progression-free survival (hazard ratio for younger age versus older age 0.933; 95% CI 0.843–1.032, $P = 0.179$).

Conclusion Metastatic colorectal cancer patients ≥ 70 years of age who are treated with 5FU-based combination chemotherapy are more likely to have serious adverse events, fatal adverse events as well as worse overall survival compared to younger patients.

Keywords Age · Prognosis · Colon cancer · Rectal cancer · Outcomes

Introduction

Management of elderly patients with metastatic colorectal cancer has always been a subject of debate [1]. While many guidelines would support aggressive chemotherapy treatment approaches in fit elderly patients, there is generally a lack of prospective evidence to support these recommendations [2]. To further complicate our assessment, many prospective studies restrict their inclusion criteria up to a certain age limit and most of the available evidence regarding outcomes of elderly patients is limited to retrospective population-based studies. Retrospective studies are generally confounded by potential biases in data collection and interpretation as well as by lack of credible collection of adverse events [3].

Previous randomized trials evaluating selected treatment approaches for elderly patients have clearly limited the selection criteria to patients considered unfit for doublet chemotherapy regimens [4]. Thus, the treatment of "fit elderly"

✉ Omar Abdel-Rahman
omar.abdelsalam@ahs.ca

[1] Department of Oncology, Cross Cancer Institute, University of Alberta, Edmonton, Alberta T4G1Z2, Canada

patients with metastatic colorectal cancer is not well-addressed in the literature [5].

In order to provide a thorough prospective assessment of the impact of age on the outcomes of metastatic colorectal cancer, a pooled assessment of the outcomes of elderly patients with metastatic colorectal cancer from different clinical trials needs to be conducted. Through this approach, we can guarantee (1) a sizable sample of elderly patients (because it is derived from multiple studies and not a single study) and (2) the fitness of included elderly patients (because of their eligibility for and inclusion into a clinical trial).

Project Data Sphere (PDS) is a platform of clinical trial de-identified dataset sharing that has been launched in the past couple of years [6]. Through this platform, access to clinical trial datasets of landmark clinical trials has been secured. This represents a clear opportunity to study the toxicity and efficacy outcomes of elderly patients with metastatic colorectal cancer treated with combination chemotherapy while avoiding (as much as we can) the confounders of population-based studies.

Objective

To assess the impact of age on toxicity and efficacy outcomes of metastatic colorectal cancer treated with 5FU-based combination chemotherapy.

Methods

Cohort selection

The current study is based on a pooled analysis of five randomized trials evaluating different 5FU-based regimens in the first-line treatment of metastatic colorectal cancer (NCT00272051; NCT00305188; NCT00115765; NCT00364013; and NCT00384176). Details of included trials were provided in Table 1. Results of primary analyses of three of the included trials were published elsewhere [7–9]. Combining the downloaded datasets of the five trials together, a total of 3223 patients were including into the current analysis.

Data collection

The following data were collected from included participants: age at randomization, body mass index, race, sex, ECOG performance status, site of the primary tumor, number of organs with distant metastases, co-treatment with oxaliplatin, bevacizumab, and/or panitumumab, co-diagnosis with diabetes, and/or hypertension. Moreover, details of different toxicities were also collected including anemia, thrombocytopenia, neutropenia, diarrhea, stomatitis, nausea, vomiting, arrhythmia, ischemic events, serious adverse events, and fatal adverse events. High-grade toxicities are defined as toxicities ≥ grade 3 (as reported in individual trial datasets).

Study end points

The following endpoints were considered in the current study:

- Rates of toxicities according to age groups (patients < 70 years versus patients ≥ 70 years).
- Overall survival (defined as the time from randomization till death from any reason). Cases who are alive at the end of the follow-up period were censored.
- Progression-free survival (defined as the time from randomization until disease progression or death). Cases who are alive at the end of the follow-up period were censored.

Statistical analysis

Chi-squared testing was used to compare baseline categorical parameters as well as different toxicities between patients < 70 years versus patients ≥ 70 years. Independent *t* test was used to compare continuous parameters between the two groups of patients.

Table 1 Description of different cohorts included in the current analysis

Study	Number of patients from each study	Start date	Completion date	Treatment regimen
(NCT00272051) *	322 (10%)	July-2002	May-2004	Control arm: FOLFOX and placebo
(NCT00305188) *	434 (13.5%)	December-2005	October-2009	Control arm: FOLFOX and placebo
(NCT00115765) (PACCE)	842 (26.1%)	June-2005	December-2009	Investigational arm: Chemotherapy and Bevacizumab and Panitumumab. Control arm: Chemotherapy and Bevacizumab.
(NCT00364013) (PRIME)	935 (29%)	August-2006	March-2013	Investigational arm: FOLFOX and Panitumumab Control arm: FOLFOX alone
(NCT00384176) (Horizon III) *	690 (21.4%)	August-2006	August-2015	Control arm: FOLFOX and bevacizumab

*In these three studies, only comparator arms were included

Table 2 Baseline characteristics of included patients (3223 patients)

Parameter	Patients < 70 years (2488 patients)	Patients ≥ 70 years (735 patients)	*P* value
BMI			
Mean (SD)	26.30 (5.20)	26.26 (4.52)	0.836
Race			
Caucasian	2243 (90.2%)	682 (92.8%)	0.063
Others	241 (9.7%)	51 (6.9%)	
Unknown	4 (0.2%)	2 (0.3%)	
Sex			
Male	1438 (57.8%)	487 (66.3%)	< 0.001
Female	1050 (42.2%)	248 (33.7%)	
ECOG score			
0	1462 (58.8%)	386 (52.5%)	0.008
1	963 (38.7%)	332 (45.2%)	
2	50 (2%)	16 (2.2%)	
Missing	13 (0.1%)	1 (0.1%)	
Primary tumor site			
Colon	1295 (52%)	431 (58.6%)	< 0.001
Rectum	617 (24.8%)	190 (25.9%)	
Unknown	576 (23.2%)	114 (15.5%)	
Number of organs with distant metastases			
1	736 (29.6%)	241 (32.8%)	< 0.001
≥ 2	1172 (47.1%)	380 (51.7%)	
Unknown	580 (23.3%)	114 (15.5%)	
Panitumumab-containing chemotherapy			
Yes	672 (27%)	217 (29.5%)	0.180
No	1816 (73%)	518 (70.5%)	
Bevacizumab-containing chemotherapy			
Yes	1238 (49.8%)	336 (45.7%)	0.054
No	1250 (50.2%)	399 (54.3%)	
Oxaliplatin-containing chemotherapy			
Yes	2351 (94.5%)	699 (95.1%)	0.419
No	132 (5.3%)	33 (4.4%)	
Unknown	5 (0.2%)	3 (0.5%)	
Diabetes mellitus			
Yes	187 (7.7%)	74 (10.2%)	0.018
No	1534 (63.3%)	422 (58%)	
Unknown	703 (29%)	231 (31.8%)	
Hypertension			
Yes	565 (22.7%)	252 (34.3%)	< 0.001
No	1220 (49%)	251 (34.1%)	
Unknown	703 (28.3%)	232 (31.6%)	

Multivariable logistic regression analysis was then used to assess the impact of age on the development of different toxicities. This analysis was adjusted for all available clinicopathological and treatment variables which include body mass index, race, sex, ECOG performance status, site of the primary tumor, number of organs with distant metastases, co-treatment with bevacizumab and/or panitumumab, and co-diagnosis with hypertension or diabetes mellitus. Multivariable Cox

Table 3 Distribution of toxicities according to age group

Parameter	Patients < 70 years	Patients ≥ 70 years	*P* value
Serious adverse events			
Yes	893 (35.9%)	352 (47.9%)	< 0.001
No	1595 (64.1%)	383 (52.1%)	
Fatal adverse events			
Yes	99 (4%)	73 (9.9%)	< 0.001
No	2389 (96%)	662 (90.1%)	
Any cardiac adverse events			
Yes	187 (7.5%)	68 (9.3%)	0.126
No	2301 (92.5%)	667 (90.7%)	
Arrhythmias			
Yes	111 (4.5%)	42 (5.7%)	0.160
No	2377 (95.5%)	693 (94.3%)	
Ischemic events			
Yes	44 (1.8%)	18 (2.5%)	0.238
No	2444 (98.2%)	717 (97.5%)	
Alopecia			
Yes	336 (13.5%)	88 (12%)	0.280
No	2155 (86.5%)	647 (88%)	
Peripheral neuropathy*			
Yes	1196 (50.9%)	356 (50.9%)	0.979
No	1155 (49.1%)	343 (49.1%)	
Diarrhea-all grade			
Yes	1417 (57%)	457 (62.2%)	0.012
No	1071 (43%)	278 (37.8%)	
Diarrhea-high grade			
Yes	287 (11.5%)	120 (16.3%)	0.001
No	2201 (88.5%)	615 (83.7%)	
Stomatitis-all grade			
Yes	611 (24.6%)	180 (24.5%)	0.970
No	1877 (75.4%)	555 (75.5%)	
Stomatitis-high grade			
Yes	40 (1.6%)	22 (3%)	0.016
No	2448 (98.4%)	713 (97%)	
Nausea/vomiting-all grade			
Yes	1544 (62.1%)	437 (59.5%)	0.203
No	944 (37.9%)	298 (40.5%)	
Nausea/vomiting-high grade			
Yes	134 (5.4%)	45 (6.1%)	0.393
No	2354 (94.6%)	690 (93.9%)	
Anemia-all grade			
Yes	389 (15.6%)	139 (18.9%)	0.035
No	2099 (84.4%)	596 (81.1%)	
Anemia-high grade			
Yes	59 (2.4%)	11 (1.5%)	0.153
No	2429 (97.6%)	724 (98.5%)	
Thrombocytopenia-all grade			
Yes	433 (17.4%)	142 (19.3%)	0.233
No	2055 (82.6%)	593 (80.7%)	
Thrombocytopenia-high grade			
Yes	54 (2.2%)	28 (3.9%)	0.016
No	2370 (97.8%)	699 (96.1%)	
Neutropenia-all grade			
Yes	1010 (40.6%)	357 (48.6%)	< 0.001
No	1478 (59.4%)	378 (51.4%)	
Neutropenia-high grade			
Yes	687 (27.6%)	258 (35.1%)	< 0.001
No	1801 (72.4%)	477 (64.9%)	
Febrile neutropenia			
Yes	60 (2.4%)	24 (3.3%)	0.202
No	2428 (97.6%)	711 (96.7%)	

*Only for patients receiving oxaliplatin-based treatment

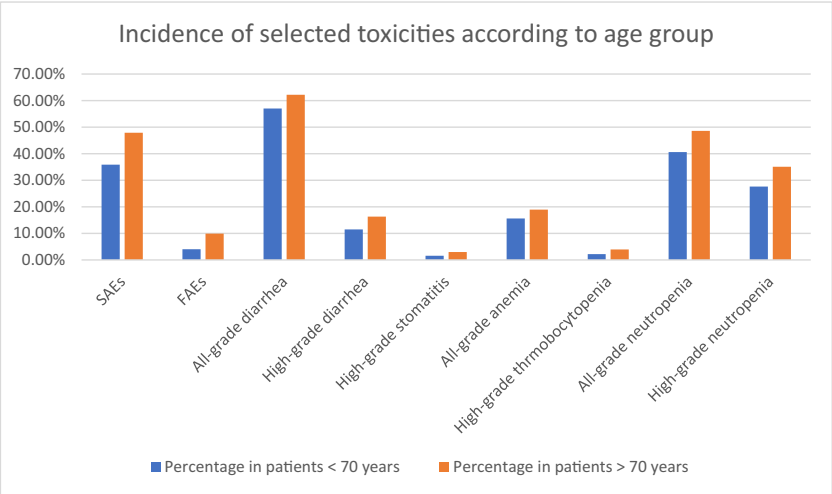

Fig. 1 Incidence of selected toxicities among younger versus older patients

regression analysis was also used to evaluate factors affecting overall and progression-free survival. This was adjusted for the same factors as in the multivariable logistic regression analysis. All statistical analyses were conducted by SPSS statistics (version 20.0, IBM, NY).

Results

Patients' characteristics

Among the total 3223 patients included in the current analysis, a total of 2488 patients were < 70 years; while 735 patients were ≥ 75 years at randomization. Mean age of the overall cohort of patients is 60.7 (SD 11.06). Comparing both groups of patients together, older patients were more likely to be males ($P < 0.001$), less likely to have ECOG performance score of 0 ($P = 0.008$), more likely to have a colon primary ($P < 0.001$), and more likely to have a co-diagnosis with diabetes ($P = 0.018$) and hypertension ($P < 0.001$). There was no difference between both groups with regard to body mass index ($P = 0.836$), race ($P = 0.063$), and co-treatment with bevacizumab ($P = 0.054$), panitumumab ($P = 0.054$), or oxaliplatin ($P = 0.419$) (Table 2). Mean follow-up duration for the overall cohort is 17.72 months (SD 10.88).

Table 4 Multivariable logistic regression analysis for the impact of age on the probability of selected toxicities

Selected toxicities*	Age	OR (95% CI)	*P* value
SAEs	≥ 70 years	Reference	< 0.001
	< 70 years	0.649 (0.545–0.772)	
FAEs	≥ 70 years	Reference	< 0.001
	< 70 years	0.416 (0.299–0.579)	
All-grade diarrhea	≥ 70 years	Reference	0.043
	< 70 years	0.834 (0.699–0.994)	
High-grade diarrhea	≥ 70 years	Reference	0.012
	< 70 years	0.734 (0.577–0.933)	
High-grade stomatitis	≥ 70 years	Reference	0.012
	< 70 years	0.500 (0.290–0.861)	
All-grade anemia	≥ 70 years	Reference	0.154
	< 70 years	0.847 (0.674–1.064)	
High-grade thrombocytopenia	≥ 70 years	Reference	0.024
	< 70 years	0.578 (0.359–0.930)	
All-grade neutropenia	≥ 70 years	Reference	< 0.001
	< 70 years	0.690 (0.578–0.824)	
High-grade neutropenia	≥ 70 years	Reference	< 0.001
	< 70 years	0.661 (0.549–0.796)	

*Each of which is adjusted for BMI, sex, race, number of metastatic sites, primary tumor location, ECOG performance score, hypertension, diabetes mellitus, bevacizumab-containing treatment, and panitumumab-containing treatment

Impact of age on the incidence of toxicities

Comparing both age groups of patients together, older patients were more likely to have a higher probability of serious adverse events ($P < 0.001$), fatal adverse events ($P < 0.001$), all-grade diarrhea ($P = 0.012$), high-grade diarrhea ($P = 0.001$), high-grade stomatitis ($P = 0.016$), all-grade anemia ($P = 0.035$), high-grade thrombocytopenia ($P = 0.016$), all-grade neutropenia ($P < 0.001$), and high-grade neutropenia ($P < 0.001$). No difference between both groups with regard to arrhythmias ($P = 0.160$), ischemic events ($P = 0.238$), alopecia ($P = 0.280$), peripheral neuropathy (among oxaliplatin-treated patients) ($P = 0.979$), all-grade stomatitis ($P = 0.970$), all-grade nausea/vomiting ($P = 0.203$), high-grade nausea/vomiting ($P = 0.393$), all-grade thrombocytopenia ($P = 0.233$), and febrile neutropenia ($P = 0.202$) (Table 3) (Fig. 1).

For specific toxicities (for which there was an evidence of age effect in the Chi-Squared testing), multivariable logistic regression analyses were conducted to assess the impact of age on the occurrence of these toxicities. Older age was associated with a higher probability of serious adverse events (OR (odds ratio) 0.649; 95% CI 0.545–0.772; $P < 0.001$), fatal adverse events (OR 0.416; 95% CI 0.299–0.579; $P < 0.001$), all-grade diarrhea (OR 0.834; 95% CI 0.699–0.994, $P = 0.043$), high-grade diarrhea (OR 0.734; 95% CI 0.577–0.933, $P = 0.012$), high-grade stomatitis (OR 0.500, 95% CI 0.290–0.861, $P = 0.012$), high-grade thrombocytopenia (OR 0.578; 95% CI 0.359–0.930, $P = 0.024$), all-grade neutropenia (OR 0.690; 95% CI 0.578–0.824, $P < 0.001$), and high-grade neutropenia (OR 0.661; 95% CI 0.549–0.796, $P < 0.001$). Older age does not seem to be associated with all-grade anemia (OR 0.847; 95% CI 0.674–1.064, $P = 0.154$) (Table 4) (Fig. 2).

Impact of age on survival outcomes

In a multivariable Cox regression analysis for factors affecting overall survival, older age was associated with worse overall survival (hazard ratio for younger age versus older age 0.848; 95% CI 0.754–0.954, $P = 0.006$). On the hand, older age was not associated with worse progression-free survival (hazard ratio for younger age versus older age 0.933; 95% CI 0.843–1.032, $P = 0.179$) (Table 5).

Discussion

The current study evaluated the impact of age on outcomes of metastatic colorectal cancer patients treated with 5FU-based combination chemotherapy. It shows that patients ≥ 70 years of age are more likely to have serious adverse events and fatal adverse events as well as worse overall survival compared with younger patients. The current analysis does not suggest that older age is associated with worse progression-free survival. The difference between overall and progression-free survival results might indicate that overall survival differences are not secondary to tumor progression but rather secondary to

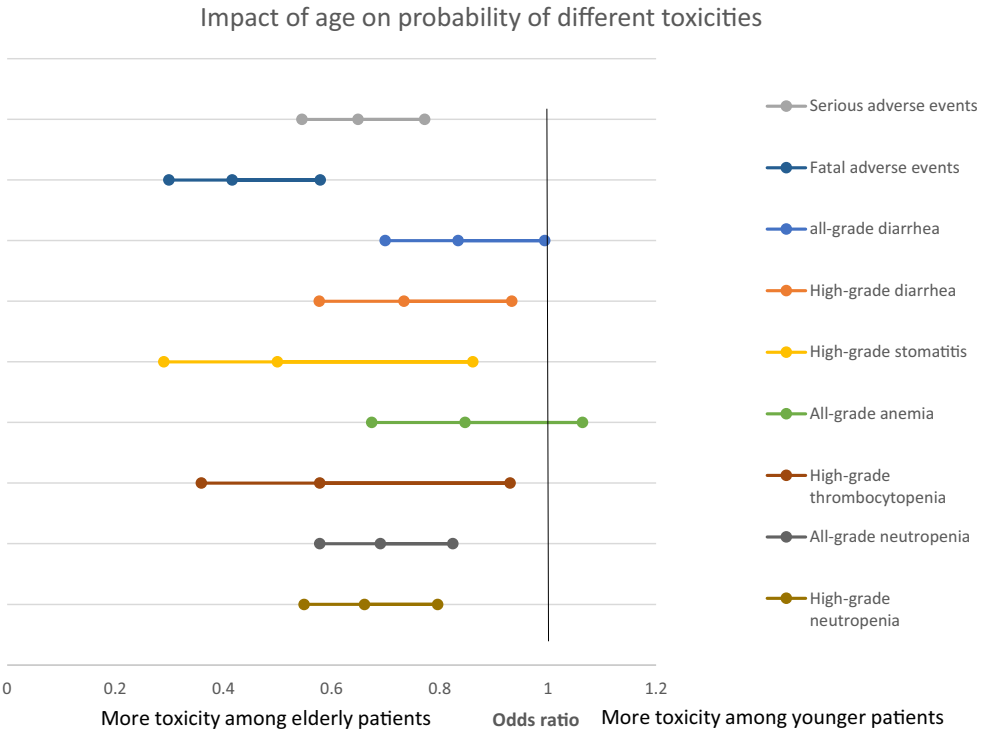

Fig. 2 Impact of age on the probability of selected toxicities

Table 5 Multivariate Cox regression analysis for the impact of age on overall and progression-free survival

Parameter*	HR (95% CI)	*P* value
i. Overall survival:		
Age		
Age ≥ 70	Reference	0.006
Age < 70	0.848 (0.754–0.954)	
ii. Progression-free survival:		
Age		
Age ≥ 70	Reference	0.179
Age < 70	0.933 (0.843–1.032)	

*Each of these analyses is adjusted for BMI, sex, race, number of metastatic sites, primary tumor location, ECOG performance score, hypertension, diabetes mellitus, bevacizumab-containing treatment, and panitumumab-containing treatment

other non-cancer related causes (e.g., co-morbidities or treatment-related mortality).

Traditional teaching in medical oncology has suggested that elderly patients with limited comorbidity and good performance status should be offered combination chemotherapy regimens like the ones recommended for younger patients [10–12]. This is somewhat challenged by the results of the current analysis. All included patients have limited comorbidity and good performance status (they have been vetted before inclusion into various clinical trials). In spite of this, there is a significant difference in the incidence of serious and fatal adverse events based on age. Thus, the current study lends support to the use of sequential single-agent treatment rather than upfront doublet or triplet chemotherapy regimens when treating elderly patients with metastatic colorectal cancer. This is further supported by prior studies showing no clear difference in overall survival between sequential single-agent chemotherapy and combination chemotherapy among patients with metastatic colorectal cancer [13, 14]. Moreover, three-drug combination regimens (incorporating bevacizumab or panitumumab) have been linked with a higher rate of toxicities (as shown in a previous pooled analysis) [15].

The current study has a number of weaknesses that have to be acknowledged; first: the primary question of the current study (impact of age on outcomes of metastatic colorectal cancer patients) was not the primary question of any of the included trials. Thus, in spite of the prospective nature of data collection of the current study cohort, it is still retrospective in nature by virtue of differences between the research questions. Second: extrapolation of the results of the current study (based on clinical trial datasets) to real-world settings should be made with caution. Third: some of the toxicities reported in the current analysis were recorded in a relatively small number of patients and this might have prevented the demonstration of subtle differences based on age. These limitations need to be assessed versus the strengths of the current study; most notably, the reliance on a prospectively collected dataset that follows the strict quality standards of clinical trials.

It is interesting to note that in contrast to the real-world setting where elderly patients represent a considerable proportion of colorectal cancer patients [16, 17], elderly patients represent only a minority among recruited patients into the five clinical trials [18–20]. This is in line with prior studies highlighting the under-representation of the elderly population in oncology clinical trials and calling for the research community to readdress this disparity [21]. We are in need to tackle elderly-specific clinical questions within dedicated clinical trials that further sub-stratify patients based on different baseline characteristics.

In conclusion, metastatic colorectal cancer patients ≥ 70 years of age who are treated with 5FU-based combination chemotherapy are more likely to have serious adverse events and fatal adverse events as well as worse overall survival compared to younger patients. Sequential single-agent strategy seems to be a safer treatment strategy among elderly patients and this needs to be assessed further in additional prospective studies.

Acknowledgments This publication is based on research using information obtained from www.projectdatasphere.org, which is maintained by the Project Data Sphere, LLC. Neither Project Data Sphere, LLC nor the owner(s) of any information from the website have contributed to, approved, or are in any way responsible for the contents of this publication.

Compliance with ethical standards

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent was obtained from all participants included in the study.

References

1. Kim JH (2015) Chemotherapy for colorectal cancer in the elderly. World J Gastroenterol 21(17):5158–5166
2. Millan M, Merino S, Caro A, Feliu F, Escuder J, Francesch T (2015) Treatment of colorectal cancer in the elderly. World J Gastrointest Oncol 7(10):204–220
3. Grande R, Natoli C, Ciancola F, Gemma D, Pellegrino A, Pavese I et al (2016) Treatment of metastatic colorectal cancer patients ≥75 years old in clinical practice: a multicenter analysis. PLoS One 11(7):e0157751-e
4. Cunningham D, Lang I, Marcuello E, Lorusso V, Ocvirk J, Shin DB, Jonker D, Osborne S, Andre N, Waterkamp D, Saunders MP (2013) Bevacizumab plus capecitabine versus capecitabine alone in elderly patients with previously untreated metastatic colorectal

cancer (AVEX): an open-label, randomised phase 3 trial. Lancet Oncol 14(11):1077–1085
5. Orum M, Gregersen M, Jensen K, Meldgaard P, Damsgaard EMS (2018) Frailty status but not age predicts complications in elderly cancer patients: a follow-up study. Acta Oncol 57(11):1458–1466
6. https://www.projectdatasphere.org/projectdatasphere/html/home. Last accessed on 7/10/2017
7. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Oliner KS, Tian Y, Xu F, Sidhu R (2014) Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 25(7):1346–1355
8. Hecht JR, Mitchell E, Chidiac T, Scroggin C, Hagenstad C, Spigel D, Marshall J, Cohn A, McCollum D, Stella P, Deeter R, Shahin S, Amado RG (2009) A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 27(5):672–680
9. Schmoll HJ, Cunningham D, Sobrero A, Karapetis CS, Rougier P, Koski SL, Kocakova I, Bondarenko I, Bodoky G, Mainwaring P, Salazar R, Barker P, Mookerjee B, Robertson J, van Cutsem E (2012) Cediranib with mFOLFOX6 versus bevacizumab with mFOLFOX6 as first-line treatment for patients with advanced colorectal cancer: a double-blind, randomized phase III study (HORIZON III). J Clin Oncol 30(29):3588–3595
10. Van Cutsem E, Cervantes A, Adam R, Sobrero A, Van Krieken JH, Aderka D et al (2016) ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 27(8):1386–1422
11. Nitsche U, Stöss C, Friess H (2017) Effect of adjuvant chemotherapy on elderly colorectal cancer patients: lack of evidence. Gastrointest Tumors 4(1–2):11–19
12. Saad AM, Abdel-Rahman O (2019) Initial systemic chemotherapeutic and targeted therapy strategies for the treatment of colorectal cancer patients with liver metastases. Expert Opin Pharmacother. https://doi.org/10.1080/14656566.2019.1642324
13. Landre T, Uzzan B, Nicolas P, Aparicio T, Zelek L, Mary F, Taleb C, Des Guetz G (2015) Doublet chemotherapy vs. single-agent therapy with 5FU in elderly patients with metastatic colorectal cancer. A meta-analysis. Int J Color Dis 30(10):1305–1310
14. Koopman M, Antonini NF, Douma J, Wals J, Honkoop AH, Erdkamp FLG, de Jong RS, Rodenburg CJ, Vreugdenhil G, Loosveld OJL, van Bochove A, Sinnige HAM, Creemers GJM, Tesselaar MET, Slee PHTJ, Werter MJBP, Mol L, Dalesio O, Punt CJA (2007) Sequential versus combination chemotherapy with capecitabine, irinotecan, and oxaliplatin in advanced colorectal cancer (CAIRO): a phase III randomised controlled trial. Lancet 370(9582):135–142
15. Abdel-Rahman O (2019) Impact of sex on chemotherapy toxicity and efficacy among patients with metastatic colorectal cancer: pooled analysis of 5 randomized trials. Clin Colorectal Cancer 18(2):110–5.e2
16. Abdel-Rahman O (2019) Outcomes of non-metastatic colon cancer patients in relationship to socioeconomic status: an analysis of SEER census tract-level socioeconomic database. Int J Clin Oncol. https://doi.org/10.1007/s10147-019-01497-9
17. Abdel-Rahman O (2018) Challenging a dogma: five-year survival does not equal cure in all colorectal cancer patients. Expert Rev Anticancer Ther 18(2):187–192
18. Abdel-Rahman O (2019) 5-fluorouracil-related cardiotoxicity; findings from five randomized studies of 5-fluorouracil-based regimens in metastatic colorectal cancer. Clin Colorectal Cancer 18(1):58–63
19. Abdel-Rahman O, Ahmed O (2019) Predictors of toxicity-related hospitalization in four randomized studies of 5-fluorouracil-based chemotherapy in metastatic colorectal cancer. Int J Color Dis 34(4):675–680
20. Abdel-Rahman O (2019) Prognostic value of baseline ALBI score among patients with colorectal liver metastases: a pooled analysis of two randomized trials. Clin Colorectal Cancer 18(1):e61–ee8
21. Le Saux O, Falandry C, Gan HK, You B, Freyer G, Péron J (2016) Inclusion of elderly patients in oncology clinical trials. Ann Oncol 27(9):1799–1804