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EDITORIAL

Do we make progress in elderly patients with metastatic colorectal cancer?

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The optimal treatment for cancer in the elderly poses problems, partly related to the underrepresentation of elderly patients in clinical trials. Colorectal cancer, especially when metastatic (mCRC), is no exception. This has been addressed in numerous articles, including reviews by the International Society of Geriatric Oncology (SIOG) [1] and by other [2]. Co-morbidities, polypharmacy, general organ deterioration, reluctance from doctors to treat, and include in trials, and different valuing of a few months longer life are reasons behind generally poorer results. Retrospective analyses of clinical trials have often reached the conclusion that elderly patients do as well as younger patients, i.e., derive similar benefits and have similar toxicity from chemotherapy [3–6]. However, a U-shaped survival curve, with the poorest survival in very young and in old patients was reported from the ARCAD (Aide et Recherche en Cancerologie Digestive) group including over 20,000 patients from 24 randomized trials [7]. Patients at the age of 57 had the lowest risk of death. It was 42% higher among the oldest, telling that old patients do not always gain as much as younger patients even if included in clinical trials.

In general, only very fit elderly patients are included in the trials and the representativity of the general population is likely minimal [6,8,9]. Marked improvements have been seen in median survival in trial patients during the past decades, presently reaching ~30 months [10,11]. The ESMO document states that 'Today, the median overall survival (OS) for patients with mCRC being treated both in phase III trials and in large observational series or registries is ~30 months and more than double that of 20 years ago'. This statement is true for a few randomized trials including selected patients with molecularly selected tumours [12,13], but is otherwise an exaggeration; it is not seen in general populations [8,14–16]. Progress has been seen also in elderly patients with CRC [17], but especially in octogenarian it is in mCRC limited to a few months in median OS, or from about 2–3 months to 3–6 months [18,19]. In this issue of Acta Oncologica, three articles bring further insight into the management of elderly patients with mCRC [20–22].

An Australian group [20] reports the outcome of the oldest mCRC patients, i.e., those over 90 years. One hundred and thirty (3%) patients out of 4199 patients belonged to this group of nonagenarian and centenarian patients. This frequency is similar to a French study [14], being 2.5% and is likely representative of western world populations. In this very old group, females with right-sided tumours dominated (over 60%), and 70% had synchronous disease, of which a quarter had their primary resected. Only 4 patients started chemotherapy, living between 5 and 14 months. Of all patients, median OS was 3 months and 10% were alive at 2 years. These figures come as no surprise, being in line with other but smaller series. The results speak against a more indolent natural course in the oldest patients, an often-held view among clinicians. The biological and molecular properties of cancers in the elderly are said to be different from those of younger individuals [23]. Of the 4 tested tumours for KRAS mutations, all were wild-type. This limited number of patients gives no real information. In a study of 503 left-sided colon cancers in patients older than 85 years, no difference in the proportions of KRAS mutations was seen compared with younger patients [24]. Neither was there any difference between those younger or older than 70 years seen in a Danish study, also reported in this issue [21].

In the Danish study [21], all 654 patients older than 50 years referred to and treated at one hospital in Copenhagen were studied. The studied population is selected, and no information about non-referred patients was available. However, it is likely that the extent of selection is less than in many other hospital-based series, and definitely than in trial populations. Twenty per cent of the referred patients older than 70 years were never treated with chemotherapy. The corresponding figure for those between 50 and 69 years was 10%. Of the treated patients, more elderly patients received monotherapy, received less often targeted agents and reduced doses were more commonly practised. Despite this, elderly patients experienced more toxicity and more frequent hospitalizations. Older patients also received fewer lines of therapy. Older patients had shorter progression-free survival (PFS), but after adjustment for co-morbidity and performance status, PFS was similar. CRC mortality did not differ.

In another article from Australia including almost 6000 patients from either a population-based register (SA) or from a treatment-related register (TRACC) [22], the proportion actively treated with chemotherapy (or surgery) clearly differs with 61% in SA, in line with what other populations registers

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have reported [8,14,15,25] and 78% in TRACC, in line with the 80% reported in the Danish study referred to above [21]. Patients with lung and liver metastases only did better than those with peritoneal metastases and particularly those with brain and skeletal metastases. Similar to another recently published Danish study [26], the relations between RAS/BRAF and MMR status and metastatic site were discussed. Although the clinical settings differed, the Australian study mainly included first-line patients and the Danish study ($n = 448$) mainly third-line patients, and the mutational analyses only done in subsets of the tumours, the overall results are rather similar. RAS mutations are associated with lung metastases and BRAF V600E mutations with peritoneal and skin metastases. Defective mismatch repair status (dMMR) appears associated with few liver-only metastases and with an increased risk of peritoneal metastases. In addition, conventional morphological criteria can indicate the metastatic pattern [27]. Thus, the two prognostic unfavourable molecular subgroups, BRAF mutations and dMMR are associated with poor prognostic metastatic locations, at least partly explaining their poor prognosis.

What do we learn from the studies about how to treat elderly patients with mCRC?

Importance of adequate referral and support

The number of aged people is growing; some talk about a 'silver tsunami' that will create a great burden on health care around the world. Elderly patients, more and more today, are sometimes very fit. The randomised trials, however, likely only including a few per cent of all eligible patients, tell that they do as well, or at least almost as well (age above 60 years was included in a nomogram recently developed by the ARCAD group to predict outcome from chemotherapy in mCRC [28]), and should receive appropriate therapy. This also includes treatment in several lines [29]. Several studies, including the Danish retrospective study [21] have shown that elderly patients receive fewer lines, even when corrected for performance status and co-morbidity. Both the Danish [21] and the Australian [22] study give no information about non-referred patients but reveal that about 20% of referred patients are not treated. This may be as expected. They may have deteriorated while waiting, being sicker than the referring surgeon thought or having contraindications not recognized, but also that they, after more thorough information, choose not to be treated. Non-treated patients were more often living alone, previously reported to be a poor prognostic sign [30]. It is important to have very short waiting times, possibly even more relevant in older than in younger patients and that the patients are actively supported.

Importance of dose intensity

Lower initial doses, generally practised by many, including the Danish study [21] will not only reduce toxicity but likely also efficacy, but is possibly better than no treatment and may well be the best for many patients. This is one important task for future pragmatic studies. A completed randomised Nordic study (Nordic 9), including 156 eligible Caucasian patients, revealed higher response rates, longer PFS, less severe toxicity with dose reduced combination chemotherapy (oxaliplatin and S1 compared with full dose monotherapy (S1) as 1st-line treatment in elderly (older than 70 years) patients not candidates for full dose combination chemotherapy [31]. S1 was prior to the Nordic 9 study favourably tested in a phase II study [32]. Further, S1 did in a Dutch randomised phase II study in Caucasian patients show similar activity to capecitabine, but with a significantly lower incidence of hand–foot syndrome [33]. Oral chemotherapy is considered important in elderly patients [34], but efficacy should not be compromised, and toxicity neither increased.

Reducing toxicity is always important, likely more so in elderly patients where palliation often is the main goal with limited possibilities for subsequent surgery. The indications to test for the presence of UGT1A1, indicating increased toxicity for irinotecan, may be more relevant in elderly patients not handling the severe toxicity as well, increasing cost-effectiveness [35].

Should bevacizumab in the absence of clear contraindications always be added to elderly patients?

Much controversy exists about the importance of adding bevacizumab to chemotherapy in mCRC and how the randomised trial data should be interpreted. Several population-based studies have shown that patients treated with bevacizumab live longer and do better than patients not receiving bevacizumab [16,36,37]. Such comparisons should always be looked at with some suspicion as bias is always present [38]. Collectively, the randomized trials indicate that the benefit is proportionally more pronounced with single-agent fluoropyrimidine than with combination chemotherapy [39–41]. As elderly patients are often treated with single-agent therapy, like in [21] and noticed in meta-analyses of the studies [42–44], the addition of bevacizumab appears more relevant than in younger patients. No OS benefit was seen in the small ($n = 102$) randomised French study PRODIGE 20 in elderly patients when combined with either single agent fluoropyrimidine or with a fluoropyrimidine doublet [45], but when the four trials assessing bevacizumab in elderly mCRC patients were combined, OS was significantly improved [43]. It should also be emphasised that no randomized study has shown that combination chemotherapy prolongs OS in elderly patients [44,46,47]. However, concerns about increased toxicity are more pronounced in elderly patients. More toxicity including arterial thromboembolic complications was also seen in elderly patients in the meta-analysis focusing on elderly patients [42]. More rare toxicities from bevacizumab may also be a concern in elderly patients [43,48,49]. Although many attempts have been done to predict benefit from bevacizumab, several reporting statistically significant associations (e.g. [50–52]), no clinically valuable marker is yet available. Bevacizumab may also induce pseudoprogression, complicating the response evaluation [53], telling that other ways of evaluating response may be important [54].

Bevacizumab has also been used as maintenance therapy, alone or in combination with most often capecitabine, again with no clear results in the trials [55]. Most evidence tells that PFS and time to failure on treatment is prolonged, whereas OS is not. Age was not relevant for the effect on PFS of maintenance bevacizumab and capecitabine in the Dutch CAIRO studies [56]; in these trials like all other studies, OS was not prolonged. Whether the effect on PFS can be ascribed to the use of bevacizumab, capecitabine or the combination is not known. The use of bevacizumab alone as maintenance in the French PRODIGE 9 study did not reveal any superiority [57].

Stratification of elderly patients?

It is evident that the old mCRC patient has great variability in how he/she will respond to the available therapy today; in one extreme they do as well as younger patients, in the other extreme, they are impossible to actively treat. Many attempts have been tried to stratify the elderly patients to personalize therapy [58,59]. It appears clear that a geriatric assessment will help in the choice of therapy, but what tool to use is still an open question, but hopefully, ongoing randomised trials will clarify this [60]. A complete geriatric assessment (CGA) likely gives the best information but is resource demanding and much easier, but still, valid instruments are required. Several attempts have been done, and they usually give clear prognostic information, at least for OS, but less so for response rate and PFS, i.e., the treatment-related outcomes [61,62]. The Nordic 9 study described above has included several geriatric measures of fitness for chemotherapy [31]. The results are awaited with interest.

Other more commonly used ways to stratify the patients is to look at tumour characteristics, laboratory values, tumour burden and metastatic sites, the latter being the topic of two of the articles in Acta Oncologica reviewed here [21,22]. These should not be forgotten when evaluating the value of the geriatric assessments.

Concluding remarks

Although much knowledge has been achieved only during the past few years in how to best treat elderly patients with mCRC, progress has been limited, particularly in prolonging OS. It is clear that 'one size does not fit all'. Whether the geriatric assessments not only hold prognostic and potentially therapy predictive value but also can direct to specific interventions aimed at improving the possibilities to actively treat elderly patients is an entirely open question. Specific trials in elderly patients are needed. A few have been done [40,46,47,63], but to improve knowledge further trials are needed, asking the important questions relevant for the elderly patients are required, some of which have been discussed above, being the focus of the three articles published in this issue of Acta Oncologica.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

[1] Papamichael D, Audisio RA, Glimelius B, et al. Treatment of colorectal cancer in older patients: International Society of Geriatric Oncology (SIOG) consensus recommendations 2013. Ann Oncol. 2015;26:463–476.

[2] Aparicio T, Francois E, Cristol-Dalstein L, et al. PRODIGE 34-FFCD 1402-ADAGE: adjuvant chemotherapy in elderly patients with resected stage III colon cancer: a randomized phase 3 trial. Dig Liver Dis. 2016;48:206–207.

[3] Folprecht G, Seymour MT, Saltz L, et al. Irinotecan/fluorouracil combination in first-line therapy of older and younger patients with metastatic colorectal cancer: combined analysis of 2,691 patients in randomized controlled trials. J Clin Oncol. 2008;26:1443–1451.

[4] Jackson NA, Barrueco J, Soufi-Mahjoubi R, et al. Comparing safety and efficacy of first-line irinotecan/fluoropyrimidine combinations in elderly versus nonelderly patients with metastatic colorectal cancer: findings from the bolus, infusional, or capecitabine with camptostar-celecoxib study. Cancer. 2009;115:2617–2629.

[5] Venderbosch S, Doornebal J, Teerenstra S, et al. Outcome of first line systemic treatment in elderly compared to younger patients with metastatic colorectal cancer: a retrospective analysis of the CAIRO and CAIRO2 studies of the Dutch Colorectal Cancer Group (DCCG). Acta Oncol. 2012;51:831–839.

[6] Mitry E, Rougier P. Review article: benefits and risks of chemotherapy in elderly patients with metastatic colorectal cancer. Aliment Pharmacol Ther. 2009;29:161–171.

[7] Lieu CH, Renfro LA, de Gramont A, et al. Association of age with survival in patients with metastatic colorectal cancer: analysis from the ARCAD Clinical Trials Program. J Clin Oncol. 2014;32:2975–2984.

[8] Sorbye H, Pfeiffer P, Cavalli-Bjorkman N, et al. Clinical trial enrollment, patient characteristics, and survival differences in prospectively registered metastatic colorectal cancer patients. Cancer. 2009;115:4679–4687.

[9] Mol L, Koopman M, van Gils CW, et al. Comparison of treatment outcome in metastatic colorectal cancer patients included in a clinical trial versus daily practice in The Netherlands. Acta Oncol. 2013;52:950–955.

[10] Cremolini C, Schirripa M, Antoniotti C, et al. First-line chemotherapy for mCRC – a review and evidence-based algorithm. Nat Rev Clin Oncol. 2015;12:607–619.

[11] Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016;27:1386–1422.

[12] Heinemann V, von Weikersthal LF, Decker T, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15:1065–1075.

[13] Venook AP, Niedzwiecki D, Lenz HJ, et al. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. JAMA. 2017;317:2392–2401.

[14] Doat S, Thiebaut A, Samson S, et al. Elderly patients with colorectal cancer: treatment modalities and survival in France. National data from the ThInDiT cohort study. Eur J Cancer. 2014;50:1276–1283.

[15] Razenberg LG, Creemers GJ, Beerepoot LV, et al. Age-related systemic treatment and survival of patients with metachronous metastases from colorectal cancer. Acta Oncol. 2016;55:1443–1449.

[16] Tomita Y, Karapetis CS, Ullah S, et al. Survival improvements associated with access to biological agents: results from the South Australian (SA) metastatic colorectal cancer (mCRC) registry. Acta Oncol. 2016;55:480–485.
[17] Braendegaard Winther S, Baatrup G, Pfeiffer P, et al. Trends in colorectal cancer in the elderly in Denmark, 1980-2012. Acta Oncol. 2016;55(Suppl 1):29–39.
[18] Sorbye H, Cvancarova M, Qvortrup C, et al. Age-dependent improvement in median and long-term survival in unselected population-based Nordic registries of patients with synchronous metastatic colorectal cancer. Ann Oncol. 2013;24:2354–2360.
[19] Mitry E, Rollot F, Jooste V, et al. Improvement in survival of metastatic colorectal cancer: are the benefits of clinical trials reproduced in population-based studies? Eur J Cancer. 2013;49: 2919–2925.
[20] Tapia Rico G, Karapetis C, Townsend AR, et al. Do we know what to do with our nonagenarian and centenarian patients with metastatic colorectal cancer (mCRC)? Results from the South Australian mCRC registry. Acta Oncol. 2018;57:1455–1457. In this issue.
[21] Lund C, Vistisen K, Dehlendorff C, et al. Age-dependent differences in first-line chemotherapy in patients with metastatic colorectal cancer: the DISCO Study. Acta Oncol. 2018;57:1445–1454. In this issue.
[22] Prasanna T, Karapetis CS, Roder D, et al. The survival outcome of patients with metastatic colorectal cancer based on the site of metastases and the impact of molecular markers and site of primary cancer on metastatic pattern. Acta Oncol. 2018;57: 1438–1444. In this issue.
[23] Patel SS, Nelson R, Sanchez J, et al. Elderly patients with colon cancer have unique tumor characteristics and poor survival. Cancer. 2013;119:739–747.
[24] Weinberg BA, Poorman K, Arguello D, et al. Impact of patient age on molecular alterations in left-sided colorectal tumors. J Clin Oncol. 2017;35:3592. Abstract 3592.
[25] Ahmed S, Pahwa P, Le D, et al. Primary tumor location and survival in the general population with metastatic colorectal cancer. Clin Colorectal Cancer. 2018;17:e201–e2e6.
[26] Christensen TD, Palshof JA, Larsen FO, et al. Associations between primary tumor RAS, BRAF and PIK3CA mutation status and metastatic site in patients with chemo-resistant metastatic colorectal cancer. Acta Oncol. 2018;57:1057–1062.
[27] Hugen N, van de Velde CJ, de Wilt JH, et al. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. Ann Oncol. 2014;25:651–657.
[28] Sjoquist KM, Renfro LA, Simes RJ, et al. Personalizing survival predictions in advanced colorectal cancer: The ARCAD Nomogram Project. J Natl Cancer Inst. 2018;110:638–648.
[29] Tampellini M, Di Maio M, Baratelli C, et al. Treatment of patients with metastatic colorectal cancer in a real-world scenario: probability of receiving second and further lines of therapy and description of clinical benefit. Clin Colorectal Cancer. 2017;16:372–376.
[30] Cavalli-Bjorkman N, Qvortrup C, Sebjornsen S, et al. Lower treatment intensity and poorer survival in metastatic colorectal cancer patients who live alone. Br J Cancer. 2012;107:189–194.
[31] Winther SB, Skuladottir H, Hofsli E, et al. NORDIC9: a randomized phase II trial comparing first-line palliative full-dose monotherapy (S-1) with reduced dose combination therapy (SOx) in older and frail patients with metastatic colorectal cancer (mCRC). Ann Oncol. 2018;29(Suppl 8): abstract 455PD.
[32] Winther SB, Zubcevic K, Qvortrup C, et al. Experience with S-1 in older Caucasian patients with metastatic colorectal cancer (mCRC): Findings from an observational chart review. Acta Oncol. 2016;55:881–885.
[33] Kwakman JJM, Simkens LHJ, van Rooijen JM, et al. Randomized phase III trial of S-1 versus capecitabine in the first-line treatment of metastatic colorectal cancer: SALTO study by the Dutch Colorectal Cancer Group. Ann Oncol. 2017;28:1288–1293.
[34] Biganzoli L, Lichtman S, Michel JP, et al. Oral single-agent chemotherapy in older patients with solid tumours: a position paper from the International Society of Geriatric Oncology (SIOG). Eur J Cancer. 2015;51:2491–2500.
[35] Butzke B, Oduncu FS, Severin F, et al. The cost-effectiveness of UGT1A1 genotyping before colorectal cancer treatment with irinotecan from the perspective of the German statutory health insurance. Acta Oncol. 2016;55:318–328.
[36] Hammerman A, Greenberg-Dotan S, Battat E, et al. The 'real-life' impact of adding bevacizumab to first-line therapy in metastatic colorectal cancer patients: a large Israeli retrospective cohort study. Acta Oncol. 2015;54:164–170.
[37] Stein A, Petersen V, Schulze M, et al. Bevacizumab plus chemotherapy as first-line treatment for patients with metastatic colorectal cancer: results from a large German community-based observational cohort study. Acta Oncol. 2015;54:171–178.
[38] Nygren P. Always look at the bright side of drugs? Acta Oncol. 2015;54:145–147.
[39] Kabbinavar FF, Hambleton J, Mass RD, et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. J Clin Oncol. 2005;23:3706–3712.
[40] Cunningham D, Lang I, Marcuello E, et al. 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. 2013;14: 1077–1085.
[41] Tebbutt NC, Wilson K, Gebski VJ, et al. Capecitabine, bevacizumab, and mitomycin in first-line treatment of metastatic colorectal cancer: results of the Australasian Gastrointestinal Trials Group Randomized Phase III MAX Study. J Clin Oncol. 2010;28: 3191–3198.
[42] Pinto C, Antonuzzo L, Porcu L, et al. Efficacy and safety of bevacizumab combined with fluoropyrimidine monotherapy for unfit or older patients with metastatic colorectal cancer: a systematic review and meta-analysis. Clin Colorectal Cancer. 2017;16: e61–e72.
[43] Koch C, Schwing AM, Herrmann E, et al. Bevacizumab-based first-line chemotherapy in elderly patients with metastatic colorectal cancer: an individual patient data based meta-analysis. Oncotarget. 2018;9:10272–10283.
[44] Landre T, Maillard E, Taleb C, et al. Impact of the addition of bevacizumab, oxaliplatin, or irinotecan to fluoropyrimidin in the first-line treatment of metastatic colorectal cancer in elderly patients. Int J Colorectal Dis. 2018;33:1125–1130.
[45] Aparicio T, Bouche O, Taieb J, et al. Bevacizumab + chemotherapy versus chemotherapy alone in elderly patients with untreated metastatic colorectal cancer: a randomized phase II trial-PRODIGE 20 study results. Ann Oncol. 2018;29:127–132.
[46] Aparicio T, Lavau-Denes S, Phelip JM, et al. Randomized phase III trial in elderly patients comparing LV5FU2 with or without irinotecan for first-line treatment of metastatic colorectal cancer (FFCD 2001-02). Ann Oncol. 2016;27:121–127.
[47] Seymour MT, Thompson LC, Wasan HS, et al. Chemotherapy options in elderly and frail patients with metastatic colorectal cancer (MRC FOCUS2): an open-label, randomised factorial trial. Lancet. 2011;377:1749–1759.
[48] Jafari M, Tessier W, El Hajbi F, et al. Delayed anastomotic leakage following bevacizumab administration in colorectal cancer patients. Acta Oncol. 2016;55:1250–1252.
[49] Bergamo F, Lonardi S, Salmaso B, et al. Angiogenesis inhibitors and symptomatic anal ulcers in metastatic colorectal cancer patients. Acta Oncol. 2018;57:412–419.
[50] Weickhardt AJ, Williams DS, Lee CK, et al. Vascular endothelial growth factor D expression is a potential biomarker of bevacizumab benefit in colorectal cancer. Br J Cancer. 2015;113: 37–45.
[51] Hagman H, Bendahl PO, Melander O, et al. Vasoactive peptides associate with treatment outcome of bevacizumab-containing therapy in metastatic colorectal cancer. Acta Oncol. 2017;56: 653–660.

[52] van Dijk E, Biesma HD, Cordes M, et al. Loss of chromosome 18q11.2-q12.1 is predictive for survival in patients with metastatic colorectal cancer treated with bevacizumab. J Clin Oncol. 2018;36: 2052–2060.

[53] Punt CJA, Huiskens J, van Gulik T, et al. Pseudoprogression on bevacizumab treatment: tumor-dynamics in the modern era of systemic treatment for metastatic colorectal cancer. Acta Oncol. 2018;57:681–682.

[54] Hermunen K, Lantto E, Poussa T, et al. Can carcinoembryonic antigen replace computed tomography in response evaluation of metastatic colorectal cancer? Acta Oncol. 2018;57:750–758.

[55] Tamburini E, Rudnas B, Santelmo C, et al. Maintenance based bevacizumab versus complete stop or continuous therapy after induction therapy in first line treatment of stage IV colorectal cancer: a meta-analysis of randomized clinical trials. Crit Rev Oncol Hematol. 2016;104:115–123.

[56] Goey KKH, Elias SG, Hinke A, et al. Clinicopathological factors influencing outcome in metastatic colorectal cancer patients treated with fluoropyrimidine and bevacizumab maintenance treatment vs observation: an individual patient data meta-analysis of two phase 3 trials. Br J Cancer. 2017;117:1768–1776.

[57] Aparicio T, Ghiringhelli F, Boige V, et al. Bevacizumab maintenance versus no maintenance during chemotherapy-free intervals in metastatic colorectal cancer: a randomized phase III trial (PRODIGE 9). J Clin Oncol. 2018;36:674–681.

[58] Aaldriks AA, Maartense E, Nortier HJ, et al. Prognostic factors for the feasibility of chemotherapy and the Geriatric Prognostic Index (GPI) as risk profile for mortality before chemotherapy in the elderly. Acta Oncol. 2016;55:15–23.

[59] Jorgensen TL, Pfeiffer P. It's time to move forward in geriatric oncology. Acta Oncol. 2016;55:1–2.

[60] Mohile SG, Dale W, Somerfield MR, et al. Practical assessment and management of vulnerabilities in older patients receiving chemotherapy: ASCO Guideline for Geriatric Oncology. J Clin Oncol. 2018;36:2326–2347.

[61] Aparicio T, Gargot D, Teillet L, et al. Geriatric factors analyses from FFCD 2001-02 phase III study of first-line chemotherapy for elderly metastatic colorectal cancer patients. Eur J Cancer. 2017; 74:98–108.

[62] Aparicio T, Bouche O, Francois E, et al. Geriatric analysis from PRODIGE 20 randomized phase II trial evaluating bevacizumab + chemotherapy versus chemotherapy alone in older patients with untreated metastatic colorectal cancer. Eur J Cancer. 2018;97:16–24.

[63] Rosati G, Cordio S, Bordonaro R, et al. Capecitabine in combination with oxaliplatin or irinotecan in elderly patients with advanced colorectal cancer: results of a randomized phase II study. Ann Oncol. 2010;21:781–786.