Adjuvant Capecitabine and Oxaliplatin for Elderly Patients with Colorectal Cancer

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Abstract
Introduction: Adjuvant chemotherapy improves the prognosis of patients with colorectal cancer (CRC) following radical resection. However, the safety and efficacy of oxaliplatin-based chemotherapeutic regimens for elderly patients remains to be elucidated. The aim of the present study was to examine the tolerability and efficacy of adjuvant CAPOX (capecitabine and oxaliplatin) therapy for elderly patients in comparison with young patients. Methods: We examined 138 Japanese patients who received adjuvant CAPOX therapy for high-risk stage II or III CRC between July 2010 and June 2021 at our hospital. Patients were divided according to an age of 70 years. Treatment details of CAPOX therapy were analyzed in association with age. Moreover, prognosis of stage III CRC was compared between the patient groups. Results: Twenty-three patients (17%) were ≥70 years old. Male patients were predominant in the ≥70 years group (p = 0.006). Patients ≥70 years old had more comorbidities (diabetes, p = 0.014; cardiovascular disease, p < 0.001; renal disease, p = 0.042) than patients <70 years old. There were no age-dependent differences in dose intensity, the number of cycles, or DLTs of CAPOX therapy. CSS and RFS were also similar between the ≥70 and <70 years old patients with stage III CRC. Conclusions: Adjuvant CAPOX therapy was tolerable in elderly Japanese patients. The prognosis of elderly patients with stage III CRC was similar to that of their younger counterparts. Advanced age itself may not be a contraindication for adjuvant chemotherapy in CRC. Future studies with a larger patient cohort are required to confirm the present results.

Introduction
Colorectal cancer (CRC) is the fourth most commonly diagnosed and the third most deadly cancer in the world [1, 2]. Previous randomized clinical trials (RCTs) revealed the efficacy of 5-fluorouracil (5-FU) at reducing the recurrence of CRC after radical resection [3–5]. Moreover, another series of RCTs showed that oxaliplatin in combination with 5-FU contributed to better survival than 5-FU alone [6–8]. Therefore, a growing number of
CRC patients are receiving oxaliplatin-based adjuvant chemotherapy [9–11].

Regarding the age-dependent efficacy of adjuvant chemotherapy, fluoropyrimidine monotherapy has been shown to effectively improve the prognosis of elderly CRC patients [12, 13]. However, the benefits of adding oxaliplatin to 5-FU for elderly CRC patients remain controversial [13–15]. Moreover, elderly patients are less frequently treated with aggressive adjuvant chemotherapy because of comorbidities, a poor performance status (PS), and concerns regarding toxicity [16, 17]. These factors may contribute to the higher rates of recurrence and mortality in older CRC patients. To establish suitable adjuvant chemotherapy regimens for the elderly, it is important to compare the treatment details of oxaliplatin-based therapy in elderly patients with those in younger patients. Furthermore, the aforementioned RCTs included only a limited number of Asian patients. Therefore, the treatment outcomes of oxaliplatin-based regimens for the elderly remain unclear.

Therefore, we herein investigated age-dependent differences in relation to dose intensity, the number of cycles, and toxicity of adjuvant CAPOX (capecitabine and oxaliplatin) therapy after radical resection. The prognosis of patients treated with adjuvant CAPOX was also analyzed in association with age.

Materials and Methods

Patients

We investigated consecutive patients who underwent radical surgery for stage II or III primary CRC and received adjuvant CAPOX therapy between July 2010 and June 2021 at the University of Tokyo Hospital. Stage II CRC patients were only included when they had high-risk features, such as T4 tumors, inadequate lymph node sampling, perforation, or a poorly differentiated histology (high-risk stage II) [9, 10, 18]. We included patients with multiple primary synchronous CRCs, colitis-associated cancer, and hereditary CRC. Patients who had previously received preoperative chemotherapy and/or radiotherapy were excluded. We also excluded patients who received fluoropyrimidine monotherapy before CAPOX, those treated with reduced doses of capecitabine and/or oxaliplatin from the first cycle, those who received preplanned short-term CAPOX (<eight cycles), or those whose adjuvant chemotherapy was terminated due to early recurrence. The present study was approved by the Ethics Committees of the University of Tokyo (No. 3252–[13]).

Adjuvant CAPOX Therapy

In our hospital, we have always recommended adjuvant chemotherapy based on the latest guidelines; currently, adjuvant CAPOX is recommended for patients who underwent radical resection for high-risk stage II and stage III CRC, according to the guidelines of the Japanese Society for Cancer of the Colon and Rectum [19]. However, adjuvant regimens were modified at doctor’s discretion, considering the patients’ age, PS, and other comorbidities. CAPOX therapy consisted of the intravenous infusion of 130 mg/m² oxaliplatin and the oral administration of capecitabine at a dose of 1,000 mg/m² twice daily for 2 weeks. The treatment course was repeated every 3 weeks [20].

Data Extraction

We retrieved the following data: sex, age, body mass index, the Eastern Cooperative Oncology Group PS, comorbidities, such as diabetes mellitus and cardiac, pulmonary, renal, and hepatic diseases; the Charlson comorbidity index (CCI) [21]; the primary location and histology; the TNM pathological classification of tumors at diagnosis according to the American Joint Committee on Cancer staging manual [22]; the relative dose intensities of chemotherapeutic drugs; the number of CAPOX cycles; completion rate of planned eight CAPOX cycles; dose reductions; treatment delays; and adverse events graded according to the Common Terminol-
ogy Criteria for Adverse Events version 5.0 [23]. Dose-limiting toxicities (DLTs) were defined as Common Terminology Criteria for Adverse Events grade 3/4 toxicities or any adverse events that contributed to unscheduled treatment delays and/or dose reductions [24].

To analyze age-dependent differences in CAPOX therapy, we divided patients into the following groups: ≥70 years and <70 years. Cancer-specific survival (CSS) and relapse-free survival (RFS) of stage III CRC patients in the two groups were also reviewed to evaluate the efficacy of CAPOX for the elders.

Table 1. Clinicopathological parameters of patients according to age

| Variable                                                   | ≥70 years (n = 23) | <70 years (n = 115) | p value |
|------------------------------------------------------------|--------------------|---------------------|---------|
| Demographic data                                           |                    |                     |         |
| Age, years                                                 | 72 (70–77)         | 56 (26–69)          | N/E     |
| Sex, male, n (%)                                           | 19 (83)            | 59 (51)             | 0.006   |
| Body mass index, kg/m²                                      | 24 (19–31)         | 22 (15–40)          | 0.063   |
| ECOG PS, n (%)                                             |                    |                     |         |
| 0                                                         | 22 (96)            | 113 (98)            | 0.42    |
| 1                                                         | 1 (4)              | 2 (2)               |         |
| Comorbidity, n (%)                                         |                    |                     |         |
| Diabetes mellitus                                          | 7 (30)             | 11 (10)             | 0.014   |
| Cardiovascular disease                                     | 15 (65)            | 29 (25)             | <0.001  |
| Pulmonary disease                                          | 2 (9)              | 9 (8)               | 1.0     |
| Renal disease                                              | 4 (17)             | 5 (4)               | 0.042   |
| Hepatic disease                                            | 0 (0)              | 0 (0)               | N/A     |
| CCI, n (%)                                                 |                    |                     |         |
| ≤1                                                        | 21 (91)            | 112 (97)            | 0.19    |
| ≥2                                                        | 2 (9)              | 3 (3)               |         |
| Tumor location, n (%)                                      |                    |                     |         |
| Colon                                                      | 13 (57)            | 69 (60)             | 0.76    |
| Rectum                                                     | 10 (43)            | 46 (40)             |         |
| Tumor histology, n (%)                                     |                    |                     |         |
| Well to moderately differentiated                          | 13 (57)            | 51 (44)             | 0.29    |
| Poorly differentiated                                      | 10 (43)            | 64 (56)             |         |
| Pathological TNM classification                             |                    |                     |         |
| T stage, n (%)                                             |                    |                     |         |
| T1                                                        | 2 (9)              | 11 (10)             | 0.43    |
| T2                                                        | 0 (0)              | 11 (10)             |         |
| T3                                                        | 14 (61)            | 53 (46)             |         |
| T4                                                        | 7 (30)             | 40 (35)             |         |
| N stage, n (%)                                             |                    |                     |         |
| N0                                                        | 3 (13)             | 10 (9)              | 0.58    |
| N1                                                        | 8 (35)             | 53 (46)             |         |
| N2                                                        | 12 (52)            | 51 (44)             |         |
| N3                                                        | 0 (0)              | 1 (1)               |         |
| Pathological stage, n (%)                                  |                    |                     |         |
| II (high-risk)                                             | 3 (13)             | 9 (8)               | 0.42    |
| III                                                       | 20 (87)            | 106 (92)            |         |
| Multiple primary CRCs                                      | 3 (13)             | 3 (3)               | 0.058   |
| Colitis-associated cancer                                  | 0 (0)              | 2 (2)               | 1.0     |
| Hereditary CRC                                             | 0 (0)              | 1 (1)               | 1.0     |

Values are presented as n (%) or median (range). ECOG PS, Eastern Cooperative Oncology Group Performance Status; CRC, colorectal cancer; N/E, not evaluated; N/A, not applicable.

Statistical analyses were performed using JMP Pro 15.0.0 (SAS Institute, Cary, NC, USA). All variables were summarized as medians (range), means ± standard deviations, or numbers (percentages). Quantitative variables were compared using the Mann-Whitney U-test. Qualitative variables were compared using Fisher’s exact test or the $\chi^2$ test with Yates’ correction. CSS and RFS were estimated by the Kaplan-Meier method and compared using the Logrank test. All reported p values were two-sided, and results were considered to be significant at a p value <0.05.
Results

A total of 138 patients who underwent CAPOX therapy were examined. Twenty-three patients (17%) were aged ≥70 years (Fig. 1). Table 1 summarizes the characteristics of patients divided according to an age of 70 years. More male patients were included in the ≥70 years group (83% vs. 51%, \( p = 0.006 \)). The majority of patients had a PS of 0, regardless of age. In addition, the number of patients with diabetes mellitus, cardiovascular disease, or renal disease was higher in the ≥70 years group than in the <70 years group (\( p = 0.014, p < 0.001, \) and \( p = 0.042, \) respectively). Only a small number of patients had CCI ≥2 in both groups (9% and 3%, respectively). No significant differences were observed in other parameters between the two groups (Table 1).

The treatment details of adjuvant CAPOX therapy are reviewed in Table 2. There was no intergroup difference in the relative dose intensity or number of cycles. The overall incidence of DLTs was 83% in the ≥70 years group and 87% in the <70 years group (\( p = 0.52 \)). Table 3 summarizes the breakdown of DLTs caused by adjuvant CAPOX; no marked differences were observed in any toxicity between the two groups.

We also compared the prognosis of stage III CRC patients who received adjuvant CAPOX therapy between

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Table 2. Treatment details of CAPOX according to age

| Variable                        | ≥70 years (n = 23) | <70 years (n = 115) | \( p \) value |
|---------------------------------|-------------------|---------------------|--------------|
| Time between radical surgery and chemotherapy, day (mean ± standard deviation) | 54.1±19.0 | 48.7±21.8 | 0.12 |
| RDI, %                          |                   |                     |              |
| Capetabinate                    | 82.1±19.4         | 86.1±21.2           | 0.22         |
| Oxaliplatin                     | 88.0±13.1         | 82.1±20.1           | 0.33         |
| Chemotherapy cycles, n          | 7 (1–8)           | 8 (1–8)             | 0.32         |
| Completion of eight cycles, n (%) | 11 (48)          | 74 (64)             | 0.16         |
| Dose reduction, n (%)           | 15 (65)           | 83 (72)             | 0.51         |
| Treatment delay, n (%)          | 18 (78)           | 83 (72)             | 0.54         |
| Grade 3/4 adverse events, n (%) | 8 (35)            | 44 (38)             | 0.75         |
| Dose limiting toxicities, n (%) | 19 (83)           | 100 (87)            | 0.52         |

Values are presented as n (%), median (range) or mean ± standard deviation. RDI, relative dose intensity.

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Fig. 2. Kaplan-Meier survival curves of stage III CRC patients treated with adjuvant CAPOX according to age. a CSS. b RFS.
the ≥70 years and <70 years groups (20 and 106 patients, respectively). The median follow-up period was 29.3 months for the ≥70 years group and 33.0 months for the <70 years group. As shown in Figure 2, there was no intergroup difference in CSS or RFS. Five-year CSS rates were 100% and 95%, and 5-year RFS rates were 84% and 75% in the ≥70 years and <70 years groups, respectively.

### Discussion

The MOSAIC trial initially reported the efficacy of an adjuvant oxaliplatin-based regimen for colon cancer using eligible patients aged ≤75 years [6]. RCTs on adjuvant oxaliplatin-based chemotherapy were subsequently conducted in Western countries by recruiting patients without age limitations [7, 8, 25, 26]. The treatment outcomes of adjuvant CAPOX/FOLFOX were compared between young and old patients in a few studies; however, the findings obtained were inconsistent [14, 15]. Furthermore, comparative outcomes among races were only reported in the XELOXA study [27]. Although several small-scale studies in Asia also investigated adjuvant CAPOX for stage III colon cancer, age-dependent differences in the treatment details of adjuvant CAPOX were not described [28–31]. The present study is the first to investigate and compare the safety and efficacy of adjuvant CAPOX therapy in elderly patients with those in younger patients in an Asian population.

A previous study reported that elderly patients with a good PS and few comorbidities were able to receive similar dose intensities of CAPOX to those of young patients [17]. In the present study, patients ≥70 years received a similar dose intensity and number of CAPOX cycles to patients <70 years. This may be partially attributed to the condition of the elderly patients examined: 22 patients (96%) had a PS of 0, while 21 (91%) had only a few comorbidities (CCI ≤1).

Regarding adverse events related to adjuvant CAPOX therapy, Schmoll et al. [20] initially reported that 355 patients aged ≥65 years showed a higher frequency of grade 3/4 adverse events than 583 patients <65 years in the XELOXA trial. However, a comprehensive analysis of four RCTs (NSABP C-08, XELOXA, X-ACT, and AVANT) demonstrated that the incidence of grade 3/4 adverse events during adjuvant oxaliplatin-including regimens was similar between age subgroups of ≥70 and <70 years (n = 477 and 2,390, respectively) [15]. Consistent with the latter findings, we herein showed that grade 3/4 adverse events and DLTs during adjuvant CAPOX were similar in elderly and younger patients.

Regarding racial discrepancies in the tolerability profiles of CAPOX, RCTs revealed that Asian patients showed less grade 3/4 toxicities than patients of other races (41–43% vs. 55–68%) [27, 32]. The frequency of grade 3/4 toxicities was also low in our cohort (37%), and in another retrospective study from China (28%) [31]. Consistent with the latter findings, we herein showed that grade 3/4 adverse events and DLTs during adjuvant CAPOX were similar in elderly and younger patients.

### Table 3. Dose limiting toxicities during adjuvant CAPOX according to age

| Variable                        | ≥70 years (n = 23) | <70 years (n = 115) | p value |
|---------------------------------|-------------------|---------------------|---------|
| Diarrhea, n (%)                 |                   |                     |         |
| DLT                             | 3 (13)            | 11 (10)             | 0.70    |
| Grade 3/4                       | 0 (0)             | 4 (3)               | 1.0     |
| Nausea/vomiting, n (%)          |                   |                     |         |
| DLT                             | 1 (4)             | 12 (10)             | 0.69    |
| Grade 3/4                       | 1 (4)             | 3 (3)               | 0.52    |
| Anorexia, n (%)                 |                   |                     |         |
| DLT                             | 5 (22)            | 19 (17)             | 0.55    |
| Grade 3/4                       | 1 (4)             | 7 (6)               | 1.0     |
| Abdominal pain, n (%)           |                   |                     |         |
| DLT                             | 1 (4)             | 2 (2)               | 0.42    |
| Grade 3/4                       | 0 (0)             | 0 (0)               | N/A     |
| Dehydration, n (%)              |                   |                     |         |
| DLT                             | 1 (4)             | 1 (1)               | 0.31    |
| Grade 3/4                       | 0 (0)             | 0 (0)               | N/A     |
| Fatigue, n (%)                  |                   |                     |         |
| DLT                             | 1 (4)             | 15 (13)             | 0.47    |
| Grade 3/4                       | 0 (0)             | 2 (2)               | 1.0     |
| Allergy, n (%)                  |                   |                     |         |
| DLT                             | 1 (4)             | 5 (4)               | 1.0     |
| Grade 3/4                       | 0 (0)             | 1 (1)               | 1.0     |
| Infection, n (%)                |                   |                     |         |
| DLT                             | 0 (0)             | 5 (4)               | 0.59    |
| Grade 3/4                       | 0 (0)             | 1 (1)               | 1.0     |
| Liver dysfunction, n (%)        |                   |                     |         |
| DLT                             | 3 (13)            | 14 (12)             | 1.0     |
| Grade 3/4                       | 1 (4)             | 4 (3)               | 1.0     |
| Hand-foot syndrome, n (%)       |                   |                     |         |
| DLT                             | 2 (9)             | 11 (10)             | 1.0     |
| Grade 3/4                       | 0 (0)             | 3 (3)               | 1.0     |
| Neurosensory toxicity, n (%)    |                   |                     |         |
| DLT                             | 4 (17)            | 24 (21)             | 1.0     |
| Grade 3/4                       | 1 (4)             | 8 (7)               | 1.0     |
| Neutropenia, n (%)              |                   |                     |         |
| DLT                             | 6 (26)            | 35 (30)             | 0.67    |
| Grade 3/4                       | 4 (17)            | 18 (16)             | 0.76    |
| Thrombocytopenia, n (%)         |                   |                     |         |
| DLT                             | 6 (26)            | 16 (14)             | 0.17    |
| Grade 3/4                       | 1 (4)             | 4 (3)               | 1.0     |

DLT, dose-limiting toxicity; N/A, not applicable.

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polymorphisms and physiological or pathological conditions, or extrinsic, including the healthcare system, dietary habits, and differences in patient recruitment by RCTs [27].

There was no age-dependent difference in the CSS or RFS of stage III CRC patients treated with adjuvant CAPOX in the present study. Therefore, CAPOX therapy may also be effective for a selected group of elderly patients. In addition, the CSS of elderly patients aged ≥70 years (5-year rate: 100%) was better than overall survival in previous RCTs (5-year rate: 69–74%) [14, 15]. This difference in survival rate may be explained by the following reasons: patients were recruited between 1997 and 2007 in these studies [14, 15], which indicates that they may not have received a number of systemic chemotherapy with biologics, such as bevacizumab, cetuximab, panitumumab, aflibercept, and ramucirumab, after relapse. Moreover, Asians, including Japanese, generally have a longer life expectancy than Caucasians, Blacks, and Hispanics [33]. A retrospective study reported longer survival in Asians with stage II/III CRC after adjuvant treatment or without chemotherapy than in other ethnicities [34].

There are several limitations that need to be addressed. This was a retrospective study that was conducted at a single hospital with a small patient cohort. A small number of patients with multiple CRCs, colitis-associated cancer, and hereditary CRC were included, and therefore, the background of patients may be heterogeneous. Moreover, the present study may have included a selection bias; adjuvant CAPOX may not have been selected for elderly patients with a poor PS or for those with severe background comorbidities. In addition, there is a possibility that the lack of difference in treatment outcomes of CAPOX between the ≥70 years and <70 years groups may be attributable to the underpower due to the small number of patients. Finally, the CSS and RFS were not fully matured in the present study.

Conclusions

In a Japanese population, adjuvant CAPOX therapy was tolerable for a select subpopulation of elderly patients. The CSS and RFS of these elderly patients were similar to those of younger patients. Although a definite conclusion cannot be drawn from this small study with patient heterogeneity, advanced age itself may not be a contraindication for adjuvant CAPOX therapy. Future studies with a larger patient cohort are required to confirm the present results.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394–424.
2 Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: incidence, mortality, survival, and risk factors. Prz Gastroenterol. 2019;14(2):89–103.
3 Laurie JA, Moertel CG, Fleming TR, Wieand HS, Leigh JE, Rubin J, et al. Surgical adjuvant therapy of largebowel carcinoma: an evaluation of levamisole and the combination of levamisole and fluorouracil. The North Central Cancer Treatment Group and the Mayo Clinic. J Clin Oncol. 1989;7(10):1447–56.
9 National Comprehensive Cancer Network.

6 André T, Boni C, Mounedji-Boudiaf L, Na-varro M, Tabernero J, Hickish T, et al. Oxali-platin, fluorouracil, and leucovorin as adju-vant treatment for colon cancer. N Engl J Med. 2004;350(23):2343–51.

7 Schmoll HJ, Tabernero J, Maroun J, de Braud F, Price T, Van Cutsem E, et al. Capicitabine plus oxaliplatin combined with fluorouracil/ folinic acid as adjuvant therapy for stage III colon cancer: final results of the NO16968 randomized controlled phase III trial. J Clin Oncol. 2015;33(32):3733–40.

Kuebler JP, Wiegand HS, O’Connell MJ, Smith RE, Colangelo LH, Yothers G, et al. Oxalipla-tin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemo-therapy for stage II and III colon cancer: re-sults from NSABP C-07. J Clin Oncol. 2007; 25(16):2198–22004.

9 National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Co-lon Cancer, version 3.2021. [Cited 2021 No-vember 15]. Available from: https://www. nccn.org/professionals/physician_gls/pdf/ colon.pdf.

10 National Comprehensive Cancer Network. Clinical practice guidelines in oncology. Rectal Cancer, version 2.2021. [Cited 2021 No-vember 15]. Available from: https://www. nccn.org/professionals/physician_gls/pdf/ rectal.pdf.

11 Osumi H, Shinozaki E, Suenaga M, Wakat-suki T, Nakayama I, Matsushima T, et al. Change in clinical outcomes during the tran-sition of adjuvant chemotherapy for stage III colorectal cancer. PLoS One. 2017;12(5): e0176745.

14 McCleary NJ, Meyerhardt JA, Green E, Yoth-ers G, de Gramont A, Van Cutsem E, et al. Impact of age on the efficacy of newer adju vant therapies in patients with stage II/III col-0ncancer: findings from the ACCENT data-base. J Clin Oncol. 2013;31(20):2600–6.

15 Haller DG, O’Connell MJ, Cartwright TH, Twelves CJ, McKenna EF, Sun W, et al. Im-pact of age and medical comorbidity on adju vant treatment outcomes for stage III colon cancer: a pooled analysis of individual patient data from four randomized, controlled trials. Ann Oncol. 2015;26(4):715–24.

16 Hoenen KJW, van Steenbergen LN, van de Wouw AJ, Rutten HJ, van Sproen DJS, Janssen-Henijn MLG. Treatment and complica-tions in elderly stage III colon cancer patients in the Netherlands. Ann Oncol. 2013;24(4): 974–9.

17 Lund CM, Nielsen D, Dehlelandorff C, Chris-tiansen AB, Raholt F, Johansen JS, et al. Ef-ficacy and toxicity of adjuvant chemotherapy in elderly patients with colorectal cancer: the ACCORE study. ESMO Open. 2016;1(5): e000087.

18 Schmoll H J, Van Cutsem E, Stein A, Valen-tini V, Gilmeilhus B, Haustermans K, et al. ESMO consensus guidelines for management of patients with colon and rectal cancer. A personalized approach to clinical decision making. Ann Oncol. 2012;23(10):2479–516.

19 Hashiguchi Y, Muro K, Saito Y, Ito Y, Ajikoa Y, Hamaguchi T, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. Int J Clin Oncol. 2020;25(1):1–42.

20 Schmoll HJ, Cartwright T, Tabernero J, Nowacki MP, Figer A, Maroun J, et al. Phase III trial of capicitabine plus oxaliplatin as ad-juvanttherapy for stage III colon cancer: a planned safetyanalysis in 1, 864 patients. J Clin Oncol. 2007;25(11):102–9.

21 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: develop-ment and validation. J Chronic Dis. 1987; 40(5):373–83.

22 Amin MB, Edge S, Greene F. AJCC cancer staging manual. 8th ed. New York, NY: Springer; 2017.

23 US Department of Health and Human Ser-vices. Common Terminology Criteria for Ad-verse Events (CTCAE), Version 5.0. [Cited 2022 February 10]. Available from: https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev5 quick_reference_5x7.pdf.

24 Prado CMM, Baracos VE, McCargar LJ, Mourtzakis M, Mulder KE, Reiman T, et al. Body composition as an independent deter-minant of 5-fluorouracil-based chemothera-py toxicity. Clin Cancer Res. 2007;13(11): 3264–8.

25 Allegra CJ, Yothers G, O’Connell MJ, Shari’i, Petrelli NJ, Colangelo LH, et al. Phase III trial assessing bevacizumab in stages II and III car-cinoma of the colon: results of NSABP protocol C-08. J Clin Oncol. 2011;29(1):11–6.

26 de Gramont A, Van Cutsem E, Schmoll HJ, Tabernero J, Clarke S, Moore MJ, et al. Beva-cizumab plus oxaliplatin-based chemothera-py as adjuvant treatment for colon cancer (AVANT): a phase 3 randomised controlled trial. Lancet Oncol. 2012;13(12):1225–33.

27 Haller DG, Cassidy J, Clarke SJ, Cunningham D, Van Cutsem E, Hoff PM, et al. Potential regional differences for the tolerability pro-files of fluoropyrimidines. J Clin Oncol. 2008; 26(13):2118–23.

28 Osawa H, Handa N, Minakata K. Efficacy and safety of capecitabine and oxaliplatin (CapOX) as an adjuvant therapy in Japanese for stage II/III colon cancer in a group at high risk of recurrence in retrospective study. On-col Res. 2015;22(5):325–31.

29 Suenaga M, Akiyoshi T, Shinozaki E, Fujimoto Y, Matussaka S, Konishi T, et al. A feasibility study of capecitabine and oxaliplatin for patients with stage II/III colon cancer -AC-TOR Study. Anticancer Res. 2018;38(3): 1741–47.

30 Danno K, Hata T, Tamai K, Fujie Y, Ide Y, Kim HM, et al. Interim analysis of a phase II trial evaluating the safety and efficacy of capecitabine plus oxaliplatin (XELOX) as adjuvant therapy in Japanese patients with operated stage III colon cancer. Cancer Chemother Pharmaco-l. 2017;80(4):777–85.

31 Chiu J, Tang V, Leung R, Wong H, Chu KW, Poon J, et al. Efficacy and tolerability of adju vant oral capicitabine plus intravenous oxali-platin (XELOX) in Asian patients with colorectal cancer: 4-year analysis. Asian Pac J Cancer Prev. 2014;14(11):6585–90.

32 Kotaka M, Yamanaka T, Yoshino T, Manaka D, Eto T, Hasegawa J, et al. Safety data from the phase III Japanese ACHIEVE trial: part of an international, prospective, planned pooled analysis of six phase III trials comparing 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer. ESMO Open. 2018;3:e000354.

33 World Health Organization. Life expectancy at birth (years). [Cited 2021 December 15]. Available from: https://www.who.int/data/ gho/data/indicators/indicator-details/GHO/ life-expectancy-at-birth.